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*Attorneys for Plaintiff
TherapeuticsMD, Inc.*

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

THERAPEUTICSMD, INC.,

Plaintiff,

v.

**AMNEAL PHARMACEUTICALS, INC.,
AMNEAL PHARMACEUTICALS, LLC,
and AMNEAL PHARMACEUTICALS OF
NEW YORK LLC,**

Defendants.

Civil Action No. _____

**COMPLAINT FOR
PATENT INFRINGEMENT**

(Filed Electronically)

Plaintiff TherapeuticsMD, Inc. (“TherapeuticsMD”), by its undersigned attorneys, for its Complaint against defendants Amneal Pharmaceuticals, Inc. (“Amneal Inc.”), Amneal Pharmaceuticals, LLC (“Amneal LLC”), and Amneal Pharmaceuticals of New York LLC (“Amneal NY”) (together, “Amneal” or “Defendants”), alleges as follows:

Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. § 100, *et seq.*, arising from the filing of Abbreviated New Drug Application (“ANDA”) No. 214293 (“Amneal’s ANDA”) with the United States Food and Drug Administration (“FDA”) seeking approval to commercially market a generic version of TherapeuticsMD’s BIJUVA[®] drug product (“Amneal’s Proposed Product”) before the expiration of United States Patent Nos. 8,633,178 (the “178 patent”); 8,846,648 (the “648 patent”); 8,846,649 (the “649 patent”); 8,987,237 (the “237 patent”); 8,993,548 (the “548 patent”); 8,993,549 (the “549 patent”); 9,006,222 (the “222 patent”); 9,114,145 (the “145 patent”); 9,114,146 (the “146 patent”); 9,301,920 (the “920 patent”); 10,052,386 (the “386 patent”); and 10,206,932 (the “932 patent”) (collectively, “the patents-in-suit”), all owned by TherapeuticsMD.

The Parties

2. Plaintiff TherapeuticsMD is a women’s healthcare company committed to creating and commercializing innovative products to support women from pregnancy prevention through menopause. TherapeuticsMD focuses on, and invests heavily in, the development and commercialization of health solutions that enable new standards of care for women.

TherapeuticsMD is a corporation organized and existing under the laws of the State of Nevada, having a principal place of business at 951 Yamato Rd., Suite 220, Boca Raton, Florida 33431.

3. On information and belief, Defendant Amneal Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 400 Crossing Boulevard, Bridgewater, New Jersey 08807.

4. On information and belief, Defendant Amneal LLC is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of

business at 400 Crossing Boulevard, Bridgewater, New Jersey 08807. On information and belief, Amneal LLC is a wholly owned subsidiary of Amneal Inc.

5. On information and belief, Defendant Amneal NY is a limited liability company organized and existing under the laws of the State of Delaware, having a place of business at 400 Crossing Blvd., Third Floor, Bridgewater, New Jersey 08807. On information and belief, Amneal NY is a wholly owned subsidiary of Amneal LLC.

The Patents-in-Suit

6. On January 21, 2014, the United States Patent and Trademark Office (“USPTO”) duly and lawfully issued the ’178 patent, entitled, “Natural Combination Hormone Replacement Formulations and Therapies,” to TherapeuticsMD as assignee of the inventors. A copy of the ’178 patent is attached hereto as Exhibit A.

7. On September 30, 2014, the USPTO duly and lawfully issued the ’648 patent, entitled, “Natural Combination Hormone Replacement Formulations and Therapies,” to TherapeuticsMD as assignee of the inventors. A copy of the ’648 patent is attached hereto as Exhibit B.

8. On September 30, 2014, the USPTO duly and lawfully issued the ’649 patent, entitled, “Natural Combination Hormone Replacement Formulations and Therapies,” to TherapeuticsMD as assignee of the inventors. A copy of the ’649 patent is attached hereto as Exhibit C.

9. On March 24, 2015, the USPTO duly and lawfully issued the ’237 patent, entitled, “Natural Combination Hormone Replacement Formulations and Therapies,” to TherapeuticsMD as assignee of the inventors. A copy of the ’237 patent is attached hereto as Exhibit D.

10. On March 31, 2015, the USPTO duly and lawfully issued the '548 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '548 patent is attached hereto as Exhibit E.

11. On March 31, 2015, the USPTO duly and lawfully issued the '549 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '549 patent is attached hereto as Exhibit F.

12. On April 14, 2015, the USPTO duly and lawfully issued the '222 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '222 patent is attached hereto as Exhibit G.

13. On August 25, 2015, the USPTO duly and lawfully issued the '145 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '145 patent is attached hereto as Exhibit H.

14. On August 25, 2015, the USPTO duly and lawfully issued the '146 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '146 patent is attached hereto as Exhibit I.

15. On April 5, 2016, the USPTO duly and lawfully issued the '920 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '920 patent is attached hereto as Exhibit J.

16. On August 21, 2018, the USPTO duly and lawfully issued the '386 patent, entitled, "Progesterone Formulations," to TherapeuticsMD as assignee of the inventors. A copy of the '386 patent is attached hereto as Exhibit K.

17. On February 19, 2019, the USPTO duly and lawfully issued the '932 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '932 patent is attached hereto as Exhibit L.

The BIJUVA[®] Drug Product

18. TherapeuticsMD holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for estradiol and progesterone capsules (NDA No. 210132), which it sells under the trade name BIJUVA[®]. BIJUVA[®] is an FDA-approved medication indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

19. The claims of the patents-in-suit cover, *inter alia*, pharmaceutical compositions and formulations comprising estradiol and progesterone, pharmaceutical compositions comprising progesterone, and methods of use of pharmaceutical compositions comprising estradiol and progesterone.

20. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the patents-in-suit are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to BIJUVA[®].

Jurisdiction and Venue

21. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

22. TherapeuticsMD received a letter from Amneal no earlier than March 17, 2020, notifying TherapeuticsMD that Amneal submitted ANDA No. 214293 (“Amneal’s Notice Letter”). Each page of Amneal’s Notice Letter bears the address 400 Crossing Boulevard, 3rd Floor, Bridgewater, NJ 08807.

23. Attached to the Amneal Notice Letter was a document entitled “Amneal Pharmaceuticals, LLC Detailed Factual and Legal Basis of Non-Infringement and/or Invalidity” (“Amneal’s Detailed Statement”).

24. On information and belief, one or more acts related to Amneal’s preparation of Amneal’s ANDA and the preparation of Amneal’s written certifications to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (“Amneal’s Paragraph IV Certification(s)”), set forth in Amneal’s ANDA were conducted in this District and/or will be conducted in the District.

25. On information and belief, upon FDA approval of Amneal’s ANDA, Amneal intends to commercially manufacture, import, market, offer for sale, and/or sell Amneal’s Proposed Product throughout the United States including in this Judicial District.

26. On information and belief, Amneal is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District. This Judicial District is a likely destination for the generic drug products described in ANDA No. 214293. On information and belief, Amneal also prepares and/or aids in the preparation and submission of ANDAs to the FDA.

27. The Court has personal jurisdiction over Amneal LLC by virtue of, *inter alia*, its continuous and systematic contacts with the State of New Jersey. On information and belief,

Amneal LLC's principal place of business is in Bridgewater, New Jersey. On information and belief, Amneal LLC is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business I.D. No. 0600211542. On information and belief, Amneal LLC is registered with the State of New Jersey's Department of Health as a drug manufacturer and wholesaler, under Registration No. 5002991. On information and belief, Amneal LLC purposefully has conducted and continues to conduct business in this Judicial District.

28. This Court has personal jurisdiction over Amneal NY because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in New Jersey, including directly or indirectly through its affiliate, agent, and/or alter ego, Amneal LLC, a company that has its principal place of business in the State of New Jersey and holds licenses with the State of New Jersey as a pharmacy wholesaler; and (2) maintains extensive and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Amneal LLC. On information and belief, Amneal NY has a place of business at 400 Crossing Blvd., Third Floor, Bridgewater, New Jersey 08807. On information and belief, Amneal NY is registered with the State of New Jersey's Department of Health as a drug manufacturer and wholesaler, under Registration No. 5003663. On information and belief, Amneal NY purposefully has conducted and continues to conduct business in this Judicial District.

29. This Court has personal jurisdiction over Amneal Inc. because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in New Jersey, including directly or indirectly through its subsidiaries, agents, and/or alter egos, Amneal LLC, a company that has its principal place of business in the State of New Jersey and holds licenses with the

State of New Jersey as a pharmacy wholesaler, and Amneal NY, a company that has a place of business in the State of New Jersey and is registered with the State of New Jersey as a drug manufacturer and wholesaler; and (2) maintains extensive and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Amneal LLC and/or Amneal NY.

30. On information and belief, Amneal Inc.'s executive offices are located in Bridgewater, New Jersey. On information and belief, Amneal Inc. owns or leases numerous properties throughout New Jersey for the purposes of manufacturing, research and development, warehousing, and packaging. (*See* Amneal Pharmaceuticals, Inc. Securities and Exchange Commission Form 10-K (for the fiscal year ended December 31, 2019) (“Amneal Inc. Form 10-K”) at 34.)

31. On information and belief, Amneal Inc. regularly and continuously transacts business within New Jersey, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey. On information and belief, Amneal Inc. derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey. Amneal Inc.'s 10-K filing states, “[t]he Company’s Generics segment includes over 200 product families covering an extensive range of dosage forms and delivery systems . . . [and] 113 products either approved but not yet launched or pending FDA approval.” (Amneal Inc. Form 10-K at 5.) On information and belief, Amneal Inc. derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

32. This Court has personal jurisdiction over Amneal because, *inter alia*, it has committed an act of patent infringement under 35 U.S.C. § 271(e)(2), and has sent notice of that

infringement to TherapeuticsMD. On information and belief, Amneal intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will continue to lead to foreseeable harm and injury to TherapeuticsMD in New Jersey and in this Judicial District. For example, on information and belief, Amneal will work towards the regulatory approval, manufacturing, use, importation, marketing, sale, offer for sale, and distribution of generic pharmaceutical products, including Amneal's ANDA Product, throughout the United States, including in New Jersey and in this Judicial District, before the expiration of the patents-in-suit.

33. In Amneal's Notice Letter, Amneal stated that the name and address of its agent in the United States authorized to accept written notice requesting access under its Office of Confidential Access is Lars Taavola, Esq., Amneal Pharmaceuticals, LLC, 400 Crossing Boulevard, 3rd Floor, Bridgewater, NJ 08807. By naming Mr. Taavola in Bridgewater, NJ as its agent in connection with this action, Amneal has consented to jurisdiction in New Jersey.

34. Amneal LLC has previously been sued in this Judicial District, has availed itself of New Jersey courts through its assertion of counterclaims in suits brought in New Jersey, and has not challenged personal jurisdiction. *See, e.g., Cubist Pharmaceuticals LLC v. Amneal Pharmaceuticals, LLC, et al.* No. 19-15439 (D.N.J.); *Senju Pharmaceutical Co., et al. v. Amneal Pharmaceuticals LLC et al.*, No. 18-05571 (D.N.J.); *BTG International Limited, et al. v. Actavis Laboratories FL, Inc., et al.*, No. 15- 05909 (D.N.J.); *Shire Pharmaceutical Development Inc., et al. v. Amneal Pharmaceuticals LLC, et al.*, No. 15-02865 (D.N.J.); *Novo Nordisk Inc., et al. v. Amneal Pharmaceuticals, LLC, et al.*, No. 13-04915 (D.N.J.); *Luitpold Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, et al.*, No. 12-05064 (D.N.J.).

35. Amneal LLC has further availed itself of the jurisdiction of this Court by initiating litigation in this Judicial District. *See, e.g., Amneal Pharmaceuticals LLC v. Reckitt Benckiser Pharmaceuticals, Inc., et al.*, No. 15-08864 (D.N.J.).

36. Amneal NY has previously been sued in this Judicial District, has availed itself of New Jersey courts through its assertion of counterclaims in suits brought in New Jersey, and has not challenged personal jurisdiction. *See, e.g., BTG International Limited et al. v. Actavis Laboratories FL, Inc.. et al.*, No. 15- 05909 (D.N.J.); *Shire Pharmaceutical Development Inc., et al. v. Amneal Pharmaceuticals LLC, et al.*, No. 15-02865 (D.N.J.); *Novo Nordisk Inc., et al. v. Amneal Pharmaceuticals, LLC, et al.*, No. 13-04915 (D.N.J.); *Luitpold Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, et al.*; No. 12-05064 (D.N.J.).

37. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and/or 1400(b).

Acts Giving Rise To This Suit

38. Pursuant to Section 505 of the FFDCA, Amneal's ANDA seeks FDA approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of 1 mg/100 mg (estradiol/progesterone) capsules before the patents-in-suit expire.

39. On information and belief, following FDA approval of Amneal's ANDA, Amneal will make, use, offer to sell, or sell Amneal's Proposed Product throughout the United States, or import such generic products into the United States.

40. On information and belief, the proposed label or proposed package insert for Amneal's Proposed Product states that it is indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

41. On information and belief, in connection with the filing of its ANDA as described above, Amneal provided Amneal's Paragraph IV Certification(s) alleging, *inter alia*, that the

claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Amneal's ANDA.

42. No earlier than March 17, 2020, TherapeuticsMD received Amneal's written notice of its Paragraph IV Certification(s). Amneal's Notice Letter alleged, *inter alia*, that the claims of the patents-in-suit are invalid and/or will not be infringed by the activities described in Amneal's ANDA. Amneal's Notice Letter also informed TherapeuticsMD that Amneal seeks approval to market Amneal's Proposed Product before the patents-in-suit expire. Amneal's Notice Letter also requested that any correspondence regarding Amneal's Offer of Confidential Access to its ANDA pursuant to 21 U.S.C. § 355(j)(5)(C) be sent to Amneal at 400 Crossing Boulevard in Bridgewater, NJ 08807.

Count I: Infringement of the '178 Patent

43. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

44. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '178 patent.

45. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

46. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '178 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

47. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '178 patent.

48. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '178 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

49. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '178 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '178 patent and knowledge that its acts are encouraging infringement.

50. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '178 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '178 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

51. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '178 patent is not enjoined.

52. TherapeuticsMD does not have an adequate remedy at law.

53. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count II: Infringement of the '648 Patent

54. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

55. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '648 patent.

56. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

57. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '648 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

58. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '648 patent.

59. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '648 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

60. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '648 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '648 patent and knowledge that its acts are encouraging infringement.

61. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '648 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '648 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

62. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '648 patent is not enjoined.

63. TherapeuticsMD does not have an adequate remedy at law.

64. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count III: Infringement of the '649 Patent

65. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

66. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '649 patent.

67. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

68. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before

the expiration of the '649 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

69. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '649 patent.

70. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '649 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

71. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '649 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '649 patent and knowledge that its acts are encouraging infringement.

72. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '649 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '649 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

73. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '649 patent is not enjoined.

74. TherapeuticsMD does not have an adequate remedy at law.

75. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IV: Infringement of the '237 Patent

76. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

77. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '237 patent.

78. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

79. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '237 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

80. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '237 patent.

81. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '237 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

82. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '237 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will

intentionally encourage acts of direct infringement with knowledge of the '237 patent and knowledge that its acts are encouraging infringement.

83. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '237 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '237 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

84. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '237 patent is not enjoined.

85. TherapeuticsMD does not have an adequate remedy at law.

86. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count V: Infringement of the '548 Patent

87. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

88. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '548 patent.

89. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

90. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '548 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

91. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '548 patent.

92. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '548 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

93. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '548 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '548 patent and knowledge that its acts are encouraging infringement.

94. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '548 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '548 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

95. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '548 patent is not enjoined.

96. TherapeuticsMD does not have an adequate remedy at law.

97. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VI: Infringement of the '549 Patent

98. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

99. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '549 patent.

100. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

101. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '549 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

102. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '549 patent.

103. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '549 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

104. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '549 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '549 patent and knowledge that its acts are encouraging infringement.

105. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '549 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '549 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

106. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '549 patent is not enjoined.

107. TherapeuticsMD does not have an adequate remedy at law.

108. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VII: Infringement of the '222 Patent

109. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

110. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial

manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '222 patent.

111. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

112. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '222 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

113. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '222 patent.

114. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '222 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

115. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '222 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '222 patent and knowledge that its acts are encouraging infringement.

116. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '222 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that

Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '222 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

117. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '222 patent is not enjoined.

118. TherapeuticsMD does not have an adequate remedy at law.

119. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VIII: Infringement of the '145 Patent

120. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

121. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '145 patent.

122. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

123. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '145 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

124. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '145 patent.

125. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '145 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

126. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '145 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '145 patent and knowledge that its acts are encouraging infringement.

127. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '145 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '145 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

128. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '145 patent is not enjoined.

129. TherapeuticsMD does not have an adequate remedy at law.

130. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IX: Infringement of the '146 Patent

131. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

132. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '146 patent.

133. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

134. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '146 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

135. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '146 patent.

136. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '146 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

137. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '146 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '146 patent and knowledge that its acts are encouraging infringement.

138. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '146 patent under 35 U.S.C. § 271(c) by

making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '146 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

139. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '146 patent is not enjoined.

140. TherapeuticsMD does not have an adequate remedy at law.

141. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count X: Infringement of the '920 Patent

142. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

143. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '920 patent.

144. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

145. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '920 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

146. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '920 patent.

147. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '920 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

148. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '920 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '920 patent and knowledge that its acts are encouraging infringement.

149. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '920 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '920 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

150. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '920 patent is not enjoined.

151. TherapeuticsMD does not have an adequate remedy at law.

152. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XI: Infringement of the '386 Patent

153. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

154. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '386 patent.

155. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

156. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '386 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

157. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '386 patent.

158. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '386 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

159. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '386 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '386 patent and knowledge that its acts are encouraging infringement.

160. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '386 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '386 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

161. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '386 patent is not enjoined.

162. TherapeuticsMD does not have an adequate remedy at law.

163. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XII: Infringement of the '932 Patent

164. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

165. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '932 patent.

166. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

167. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before

the expiration of the '932 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

168. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '932 patent.

169. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '932 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

170. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '932 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '932 patent and knowledge that its acts are encouraging infringement.

171. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '932 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '932 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

172. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '932 patent is not enjoined.

173. TherapeuticsMD does not have an adequate remedy at law.

174. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff TherapeuticsMD respectfully requests the following relief:

(A) A Judgment that Amneal has infringed the patents-in-suit by submitting ANDA No. 214293;

(B) A Judgment that Amneal has infringed, and that Amneal's making, using, offering to sell, selling, or importing Amneal's Proposed Product will infringe one or more claims of the patents-in-suit;

(C) An Order that the effective date of FDA approval of ANDA No. 214293 be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which TherapeuticsMD is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Amneal and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing Amneal's Proposed Product until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which TherapeuticsMD is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Amneal, its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from practicing any of the claimed inventions of the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which TherapeuticsMD is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Amneal's Proposed Product will directly infringe, induce, and/or contribute to infringement of the patents-in-suit;

(G) To the extent that Amneal has committed any acts with respect to the claimed inventions of the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding TherapeuticsMD damages for such acts;

(H) If Amneal engages in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Amneal's Proposed Product before the expiration of the patents-in-suit, a Judgment awarding damages to TherapeuticsMD resulting from such infringement, together with interest;

(I) A Judgment declaring that the patents-in-suit remain valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding TherapeuticsMD its attorneys' fees incurred in this action;

(K) A Judgment awarding TherapeuticsMD its costs and expenses incurred in this action; and

(L) Such further and other relief as this Court may deem just and proper.

Dated: April 29, 2020

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: April 29, 2020

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EXHIBIT A



US008633178B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 8,633,178 B2**
(45) **Date of Patent:** **Jan. 21, 2014**

(54) **NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

(71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL
(US)

(72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US);
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FL (US)

(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL
(US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/684,002**

(22) Filed: **Nov. 21, 2012**

(65) **Prior Publication Data**

US 2013/0129818 A1 May 23, 2013

Related U.S. Application Data

(60) Provisional application No. 61/563,408, filed on Nov.
23, 2011, provisional application No. 61/661,302,
filed on Jun. 18, 2012, provisional application No.
61/662,265, filed on Jun. 20, 2012.

(51) **Int. Cl.**
A01N 45/00 (2006.01)
A61K 9/48 (2006.01)

(52) **U.S. Cl.**
USPC **514/169; 424/452**

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are pro-
vided herein. Among others, the following formulations are
provided herein: solubilized estradiol without progesterone;
micronized progesterone without estradiol; micronized
progesterone with partially solubilized progesterone; solubi-
lized estradiol with micronized progesterone; solubilized
estradiol with micronized progesterone in combination with
partially solubilized progesterone; and solubilized estradiol
with solubilized progesterone.

6 Claims, 4 Drawing Sheets

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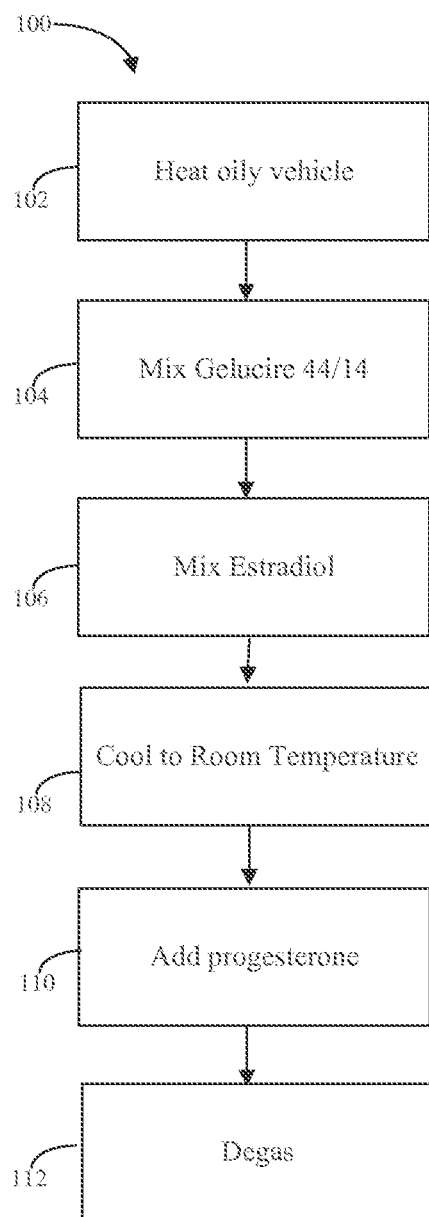


Fig. 1

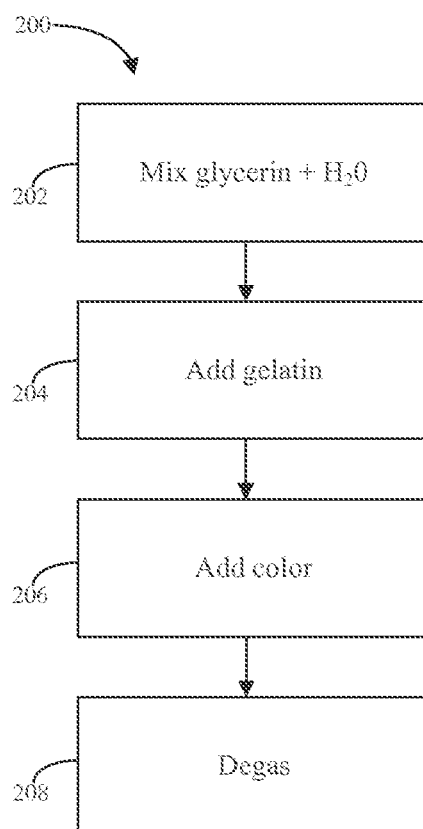


Fig. 2

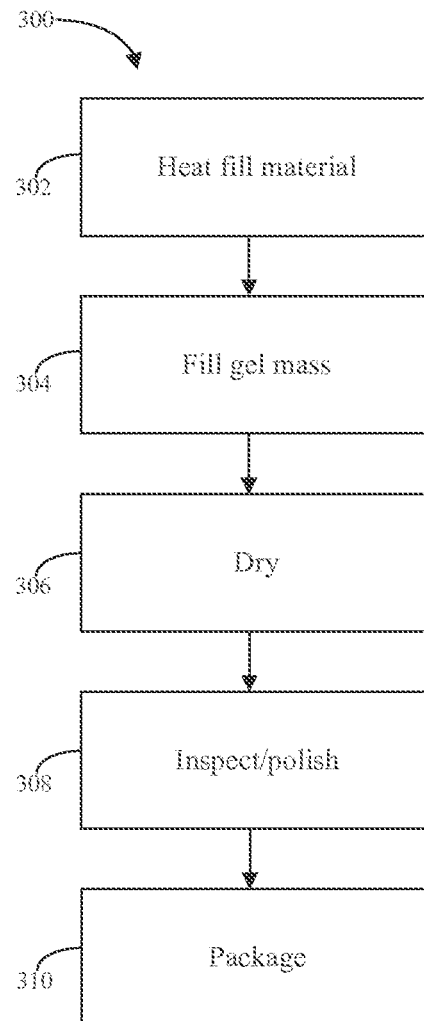


Fig. 3

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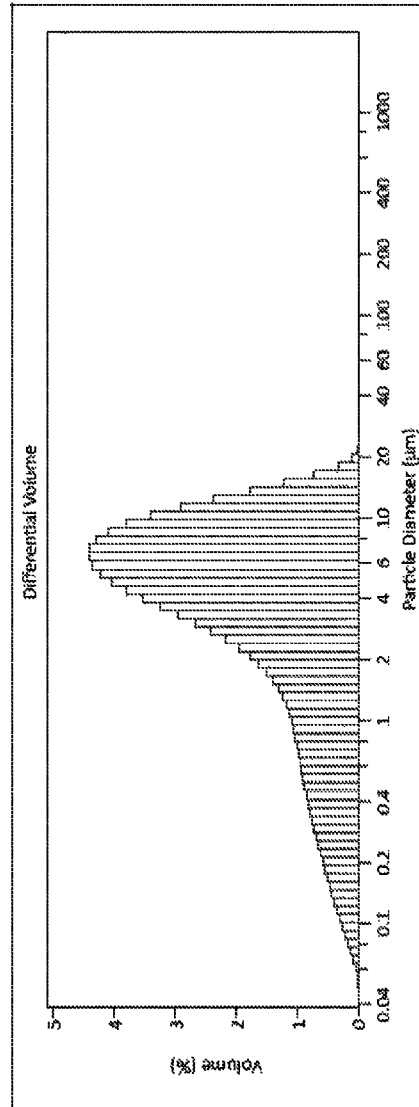


FIG. 4

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NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a nonprovisional application of and claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and 3. U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

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"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as PREM-PRO (conjugated estrogens/medroxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens plus medroxyprogesterone acetate tablets) (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN (conjugated estrogens tablets) (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

DEFINITIONS

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to PROMETRIUM (progesterone, USP) at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, T_{max} .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ C_{max} ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ T_{max} ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to estab-

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lished governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

Description

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM (progesterone, USP) when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of

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progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of PROMETRIUM (progesterone, USP). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM (progesterone, USP) equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM (progesterone, USP) can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125,

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1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μ m to 2000 μ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

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Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE (a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride); SASOL Germany GMBH, Hamburg; MIGLYOL (caprylic/capric triglyceride) includes MIGLYOL 810 (Caprylic/Capric Triglyceride), MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 816 (Caprylic/Capric Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL PG-10 (Propylene Glycol Monocaprate); the CAPMUL brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM (Medium Chain Mono- and Diglycerides)); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL (diethylene glycol mono ester)); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL (caprylic/capric triglyceride); TRANSCUTOL (Diethylene glycol monoethyl ether), MIGLYOL (caprylic/capric triglyceride) and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant; and CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for full solubilization of progesterone. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride) can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone

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per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

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As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the com-

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monly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL HP	141
(Highly purified diethylene glycol monoethyl ether EP/NF)	
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	31.2

*Literature reference—Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) at 50%; and also CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL PG-8 (Propylene Glycol Monocaprylate) mixed with MIGLYOL (caprylic/capric triglyceride) at the 15 and 30% level did not provide sufficient solubility.

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TABLE 2

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (85:15)	4.40
MIGLYOL (caprylic/capric triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	8.60
TRANSCUTOL (Diethylene glycol monoethyl ether) MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	>12
TRANSCUTOL (Diethylene glycol monoethyl ether) MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	>12
MIGLYOL (caprylic/capric triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	14.0
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	19.8
polysorbate 80: CAPMUL MCM (Medium Chain Mono- and Diglycerides) (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. MIGLYOL 812 (Caprylic/Capric Triglyceride) with 4% 30 TRANSCUTOL (Diethylene glycol monoethyl ether) precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL (caprylic/capric triglyceride): CAPMUL (a propylene glycol monocaprylate; propylene glycol monocaprylate) blends at 30 and 50% or in CAPMUL 35 MCM (Medium Chain Mono- and Diglycerides) alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
TRANSCUTOL (Diethylene glycol monoethyl ether) MIGLYOL 812 (Caprylic/ Capric Triglyceride) (4:96)	4	Crystallizes after 96 hours
MIGLYOL 812 (Caprylic/ Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/ Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	6	Clear, after 14 days
TRANSCUTOL (Diethylene glycol monoethyl ether) MIGLYOL 812 (Caprylic/ Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	6	Clear, after 14 days
CAPMUL MCM(Medium Chain Mono- and Diglycerides)	6	Clear, after 14 days

12 mg estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) 50:50, CAPMUL MCM (Medium Chain Mono- and Diglycerides), and in mixtures of TRANSCUTOL (Diethyl-

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ene glycol monoethyl ether):MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
MIGLYOL 812 (Caprylic/ Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether) MIGLYOL 812 (Caprylic/ Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL 812 (Caprylic/ Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	12	Clear, after 12 days
CAPMUL MCM(Medium Chain Mono- and Diglycerides)	12	Clear, after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization. All CAPMUL PG-8 (Propylene Glycol Monocaprylate) containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL PG-8 (Propylene Glycol Monocaprylate) alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
MIGLYOL 812 (Caprylic/ Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25)	6	Precipitated
MIGLYOL 812 (Caprylic/ Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Hazy

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TABLE 5-continued

Formulation	Estradiol mg/g	Results after addition of 7% water
TRANSCUTOL (Diethylene glycol monoethyl ether):	12	Hazy
MIGLYOL 812 (Caprylic/Capric Triglyceride):		
CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear
CAPMUL MCM(Medium Chain Mono- and Diglycerides)		
TRANSCUTOL (Diethylene glycol monoethyl ether)	12	Hazy
MIGLYOL 812 (Caprylic/Capric Triglyceride):		
CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)		

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (TRANSCUTOL HP) (Highly purified diethylene glycol monoethyl ether EP/NF)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM) (Medium Chain Mono- and Diglycerides)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

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In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM) (Medium Chain Mono- and Diglycerides)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL (caprylic/capric triglyceride) was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL (caprylic/capric triglyceride) may be used in embodiments comprising a suspension of progesterone, though MIGLYOL (caprylic/capric triglyceride), standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM (Medium Chain Mono- and Diglycerides) is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL (caprylic/capric triglyceride) had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL MCM (Medium Chain Mono- and Diglycerides). It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL MCM (Medium Chain Mono- and Diglycerides).

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TABLE 9

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	73.4
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	95
MIGLYOL 812 (Caprylic/Capric Triglyceride)	27.8

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM (Medium Chain Mono- and Diglycerides) in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Gelucire 44/14 system, wherein the ratio of CAPMUL MCM (Medium Chain Mono- and Diglycerides) to GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides): GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG) (9:1))	86.4
CAPMUL MCM (Medium Chain Mono- and Diglycerides): GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG) (7:3))	70.5
CAPMUL MCM (Medium Chain Mono- and Diglycerides): GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (6:4)	57.4

Example 7

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97
GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this

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Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL MCM (Medium Chain Mono- and Diglycerides) may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/- 2° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) may be added to the CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Heat may be removed from the GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 Caprylic/Capric Triglyceride) or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL (caprylic/capric triglyceride) MIGLYOL is heated to about 45° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

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TABLE 13

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/ diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM) (Medium Chain Mono- and Diglycerides)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32 glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to about 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride MIGLYOL 812 (Caprylic/ Capric Triglyceride) or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32 glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	300	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL (caprylic/capric triglyceride) may be present in a range from about 35-95% by weight; GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API com-

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prising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μm , an X75 of 7.442 μm , and an X25 of 1.590 μm . The Beckman Device also yielded that the mean particle size is 4.975 μm , the median particle size is 4.279 μm , the mode particle size is 6.453 μm , and the standard deviation is 3.956 μm . A graph of the particle distribution obtained is shown in FIG. 4.

Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μm , an X75 of 17.3 μm , and an X25 of 5.3 μm . The Beckman Device also yielded that the mean particle size is 11.8 μm , the median particle size is 11.04 μm , the mode particle size is 13.6 μm , and the standard deviation is 7.8 μm .

Example 12

In order to increase the solubility of progesterone in the final solution, GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97	5.78
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) Gelucire 44/14, NF		10.0	70.00	0.70
Total:		100.00		700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 40° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

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Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		73.371	146.74	1467.42
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.500	3.00	30.00
Total:			100.000	200.00 mg	2000.00

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		65.32	391.93	3919.3
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

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Example 15

Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM (progesterone, USP) (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM (progesterone, USP) soft gel Capsule 200 mg and ESTRACE (estradiol vaginal cream, USP, 0.01%) ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

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All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of $-70^{\circ}\text{C} \pm 20^{\circ}\text{C}$ in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to $40^{\circ}\text{C} \pm 5^{\circ}\text{C}$. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 .

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any

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suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Heating may be performed until the temperature reaches $80^{\circ}\text{C} \pm 5^{\circ}\text{C}$.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to $30^{\circ}\text{C} \pm 3^{\circ}\text{C}$. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes. Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of $55^{\circ}\text{C} \pm 10^{\circ}\text{C}$. The wedge temperature may be $38^{\circ}\text{C} \pm 3^{\circ}\text{C}$. The drum cooling temperature may be $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$. The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness $0.85\text{ mm} \pm 0.05\text{ mm}$ using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight $\pm 5\%$ (i.e., $650 \pm 33\text{ mg}$ and $325 \pm 16.3\text{ mg}$).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A pharmaceutical formulation comprising solubilized estradiol, suspended progesterone, and a medium chain solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed;

wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises a C6-C12 oil.

2. The pharmaceutical formulation of claim 1, further comprising partially solubilized progesterone.

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3. The pharmaceutical formulation of claim 1, wherein the formulation is contained within a gelatin capsule.

4. The pharmaceutical formulation of claim 1, wherein the medium chain solubilizing agent is selected from at least one of mono-, di-, and triglycerides and combinations thereof. 5

5. The pharmaceutical formulation of claim 1, wherein said estrogen has a dosage strength at least about 0.125 mg and wherein said progesterone has a dosage strength at least about 25 mg.

6. The pharmaceutical formulation of claim 1, wherein the 10 ratio of progesterone to estradiol is at least 95:1.

* * * * *

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,633,178 B2
APPLICATION NO. : 13/684002
DATED : January 21, 2014
INVENTOR(S) : Brian A. Bernick et al.

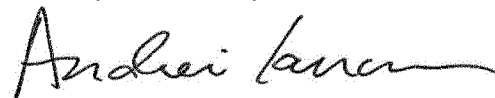
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,633,178 B2
APPLICATION NO. : 13/684002
DATED : January 21, 2014
INVENTOR(S) : Brian A. Bernick et al.

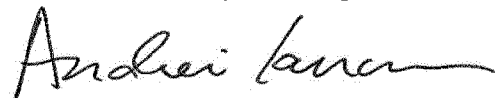
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 23, Claim 5, Line 7: Delete “estrogen” and insert in its place --estradiol--.

Signed and Sealed this
Twentieth Day of August, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu", written in a cursive style.

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT B



US008846648B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 8,846,648 B2**
(45) **Date of Patent:** ***Sep. 30, 2014**

- (54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**
- (71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)
- (72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US); **Janice Louise Cacace**, Miami, FL (US); **Peter H. R. Persicaner**, Boca Raton, FL (US); **Neda Irani**, Palm Beach Garden, FL (US); **Julia M. Amadio**, Boca Raton, FL (US)
- (73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
This patent is subject to a terminal disclaimer.
- (21) Appl. No.: **14/099,545**
- (22) Filed: **Dec. 6, 2013**

(65) **Prior Publication Data**
US 2014/0088051 A1 Mar. 27, 2014

- Related U.S. Application Data**
- (62) Division of application No. 13/684,002, filed on Nov. 21, 2012, now Pat. No. 8,633,178.
- (60) Provisional application No. 61/662,265, filed on Jun. 20, 2012, provisional application No. 61/661,302, filed on Jun. 18, 2012, provisional application No. 61/563,408, filed on Nov. 23, 2011.

- (51) **Int. Cl.**
A01N 45/00 (2006.01)
A61K 9/48 (2006.01)
A61K 31/565 (2006.01)
A61K 9/16 (2006.01)
A61K 31/57 (2006.01)

- (52) **U.S. Cl.**
CPC **A61K 31/57** (2013.01); **A61K 9/4858** (2013.01); **A61K 31/565** (2013.01); **A61K 9/16** (2013.01)
USPC **514/169**; 424/452
- (58) **Field of Classification Search**
USPC 514/169
See application file for complete search history.

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Primary Examiner — Frederick Krass

Assistant Examiner — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton LLP; Marian D. Walker

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

20 Claims, 4 Drawing Sheets

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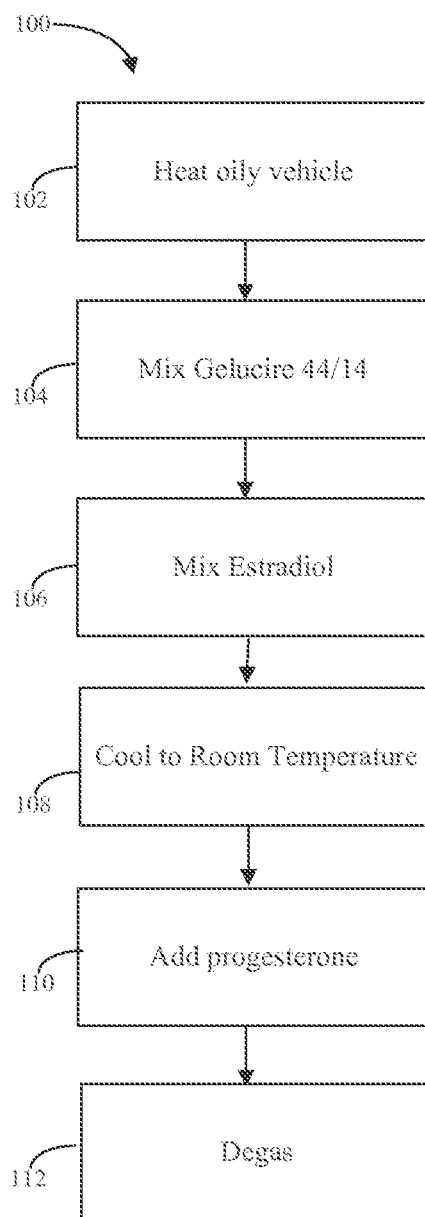


Fig. 1

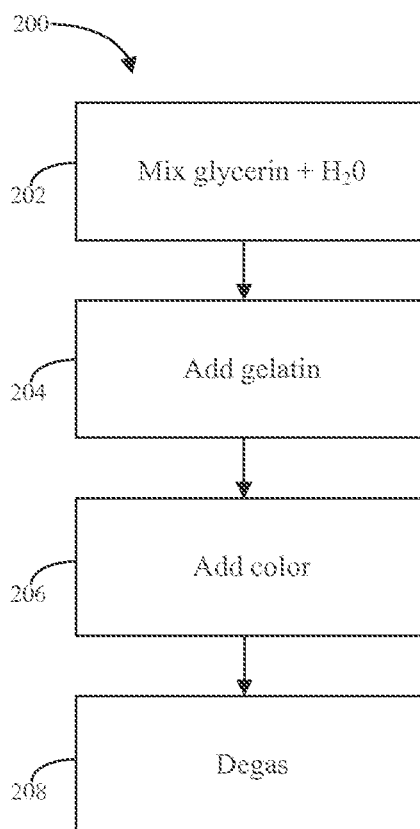


Fig. 2

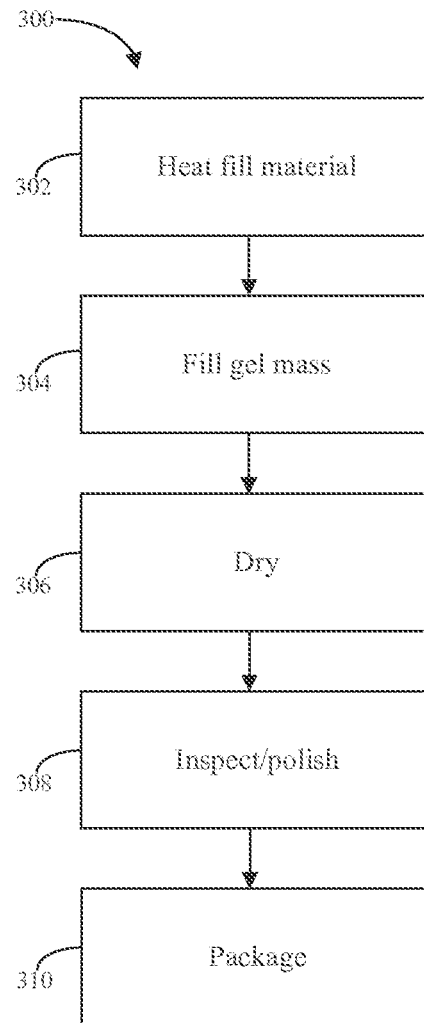


Fig. 3

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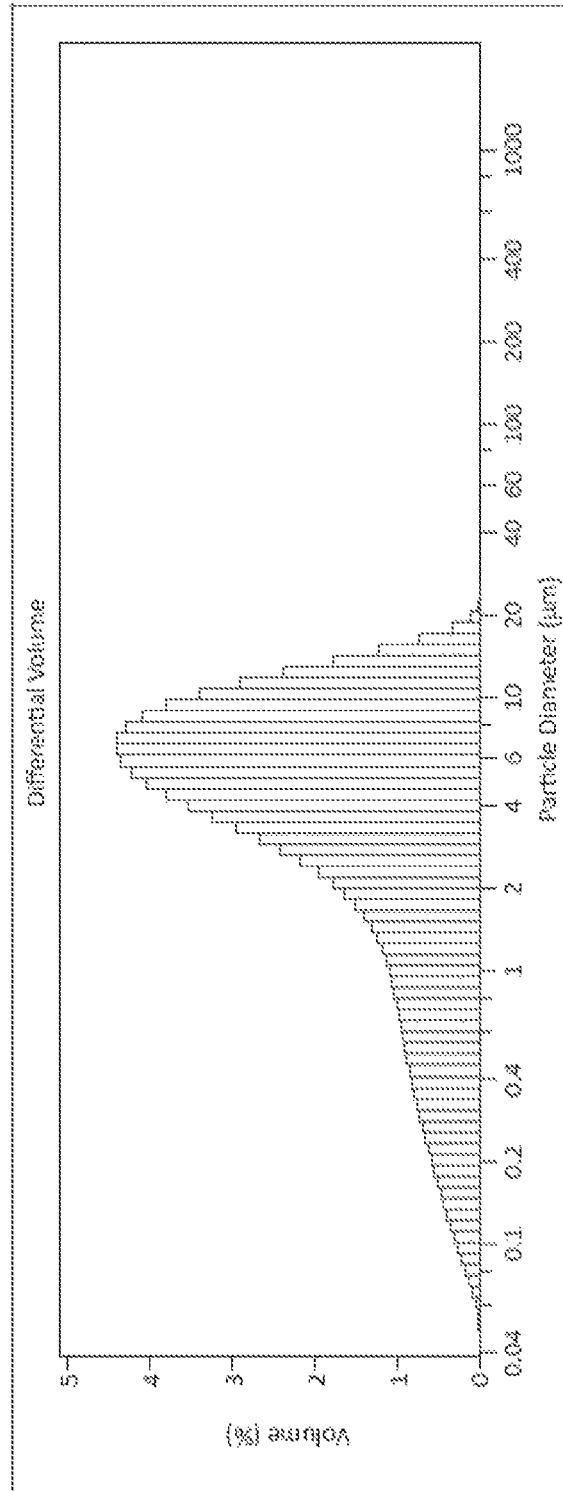


FIG. 4

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NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a non-provisional application of and claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

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"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as PREM-PRO (conjugated estrogens/medroxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens plus medroxyprogesterone acetate tablets) (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN (conjugated estrogens tablets) (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

Definitions

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that

ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to PROMETRIUM (progesterone, USP) at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, T_{max} .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ C_{max} ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ T_{max} ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

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The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

Description

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM (progesterone, USP) when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg:50 mg to about 2 mg:1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal

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dosages of PROMETRIUM (progesterone, USP). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM (progesterone, USP) at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM (progesterone, USP) can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary

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dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μ m to 2000 μ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil;

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generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE (a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride); SASOL Germany GMBH, Hamburg; MIGLYOL (caprylic/capric triglyceride) includes MIGLYOL 810 (Caprylic/Capric Triglyceride), MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 816 (Caprylic/Capric Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL PG-10 (Propylene Glycol Monocaprate); the CAPMUL brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM (Medium Chain Mono- and Diglycerides)); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL (diethylene glycol mono ester)); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL (caprylic/capric triglyceride); TRANSCUTOL (Diethylene glycol monoethyl ether), MIGLYOL (caprylic/capric triglyceride) and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant; and CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for full solubilization of progesterone. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride) can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be

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solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

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As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate,

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medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF)	141
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	31.2

*Literature reference - Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) at 50%; and also CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL PG-8 (Propylene Glycol Monocaprylate) mixed with MIGLYOL (caprylic/capric triglyceride) at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (85:15)	4.40

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TABLE 2-continued

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	8.60
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	>12
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	>12
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	14.0
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	19.8
Polysorbate 80:CAPMUL MCM (Medium Chain Mono- and Diglycerides) (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. MIGLYOL 812 (Caprylic/Capric Triglyceride) with 4% TRANSCUTOL (Diethylene glycol monoethyl ether) precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL (a propylene glycol monocaprylate; propylene glycol monocaprylate) blends at 30 and 50% or in CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride) (4:96)	4	Crystallizes after 96 hours
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	6	Clear, after 14 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	6	Clear, after 14 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	6	Clear after 14 days

12 mg estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate)

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prylate) 50:50, CAPMUL MCM (Medium Chain Mono- and Diglycerides), and in mixtures of TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Clear, after 12 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization. All CAPMUL PG-8 (Propylene Glycol Monocaprylate) containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL PG-8 (Propylene Glycol Monocaprylate) alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25)	6	Precipitated
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Hazy

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TABLE 5-continued

Formulation	Estradiol mg/g	Results after addition of 7% water
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Hazy
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF))	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	322.97	99.38	3.23 kg
Total		100	3.25 kg

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The above formulation is prepared as follows: estradiol is added to CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL (caprylic/capric triglyceride) was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL (caprylic/capric triglyceride) may be used in embodiments comprising a suspension of progesterone, though MIGLYOL (caprylic/capric triglyceride), standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM (Medium Chain Mono- and Diglycerides) is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL (caprylic/capric triglyceride) had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL MCM (Medium Chain Mono- and Diglycerides). It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL MCM (Medium Chain Mono- and Diglycerides).

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	73.4
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	95
MIGLYOL 812 (Caprylic/Capric Triglyceride)	27.8

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM (Medium Chain Mono- and Diglycerides) in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Gelucire 44/14 system, wherein the ratio of CAPMUL MCM (Medium Chain Mono- and Diglycerides) to GELUCIRE 44/14 (Lauroyl macrogol-

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32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (9:1)	86.4
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (7:3)	70.5
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (6:4)	57.4

Example 7

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97
GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL MCM (Medium Chain Mono- and Diglycerides) may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/- 2° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) may be added to the CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Heat may be removed from the GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) and

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CAPMUL MCM (Medium Chain Mono- and Diglycerides) mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL (caprylic/capric triglyceride) is heated to about 45° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2%

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w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to about 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL (caprylic/capric triglyceride) may be present in a range from about 35-95% by weight; GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 µm, an X75 of 17.3 µm, and an X25 of 5.3 µm. The Beckman Device also yielded that the mean particle size is 11.8 µm, the median particle size is 11.04 µm, the mode particle size is 13.6 µm, and the standard deviation is 7.8 µm.

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Example 12

In order to increase the solubility of progesterone in the final solution, GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
15	1. Progesterone, USP, micronized	50.00	7.14	50.00	0.50
	2. Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
	3. CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97	5.78
20	4. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG))		10.0	70.00	0.70
25	Gelucire 44/14, NF				
30	Total:	100.00	700.00	7.00	

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 40° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
50	1. Progesterone, USP, micronized	50.00	25.000	50.00	500.00
	2. Estradiol Hemihydrate	0.25	0.129	0.26	2.58
	3. CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		73.371	146.74	1467.42
55	4. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.500	3.00	30.00
60	Total:	100.000	200.00 mg	2000.00	

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C.

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GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33 200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35 2.07	20.7
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		65.32 391.93	3919.3
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.00 6.0	60.0
Total:		100.00	600.0 mg	6000.0

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

Progesterone and Estradiol Combination Study under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM (progesterone, USP) (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

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Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM (progesterone, USP) soft gel Capsule 200 mg and ESTRACE (estradiol vaginal cream, USP, 0.01%) (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ±20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration

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of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+/-3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled

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volumes. Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/-10° C. The wedge temperature may be 38° C.+/-3° C. The drum cooling temperature may be 4° C.+/-2° C. The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/-10° C. The wedge temperature may be 38° C.+/-3° C. The drum cooling temperature may be 4° C.+/-2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A method of treating a menopause-related symptom in a woman comprising:

administering to the woman an effective amount of a pharmaceutical composition, the pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed;

wherein the solubilizing agent contains an effective amount of C6-C12 oil; and

wherein at least about 90% of the estradiol is solubilized in the solubilizing agent.

2. The method of claim 1, further comprising partially solubilized progesterone, the partially solubilized progesterone being solubilized in the solubilizing agent.

3. The method of claim 1, wherein the composition is formulated as a gelatin capsule.

4. The method of claim 1, wherein the C6-C12 oil is selected from at least one of mono-, di-, and triglycerides and combinations thereof.

5. The method of claim 1, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

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6. The method of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

7. The method of claim 1, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and to a 2 mg estradiol tablet.

8. A method of treating a menopause symptom in a woman comprising administering a pharmaceutical composition to the woman, the pharmaceutical composition comprising:

solubilized estradiol;

suspended progesterone; and

a solubilizing agent, the solubilizing agent containing an effective amount of a C6-C12 oil;

wherein the estradiol and the suspended progesterone are present in the solubilizing agent, the estradiol and the suspended progesterone are uniformly dispersed and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the estradiol does not precipitate for at least 14 days.

9. The method of claim 8, further comprising partially solubilized progesterone, the partially solubilized progesterone being solubilized in the solubilizing agent.

10. The method of claim 8, wherein the composition is formulated as a gelatin capsule.

11. The method of claim 8, wherein the C6-C12 oil is selected from at least one of mono-, di-, and triglycerides and combinations thereof.

12. The method of claim 8, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

13. The method of claim 8, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

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14. The method of claim 8, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and to a 2 mg estradiol tablet.

15. A method of treating a menopause symptom comprising:

administering an effective amount of a pharmaceutical composition to a woman, the pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent, the estradiol being stable in the solubilizing agent for at least 14 days; wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed;

wherein at least about 90% of the estradiol is solubilized in the solubilizing agent, and wherein the solubilizing agent contains an effective amount of a C6-C12 oil.

16. The method of claim 15, further comprising partially solubilized progesterone, the partially solubilized progesterone being solubilized in the solubilizing agent.

17. The method of claim 15, wherein the composition is formulated as a gelatin capsule.

18. The method of claim 15, wherein the C6-C12 oil is selected from at least one of mono-, di-, and triglycerides and combinations thereof.

19. The method of claim 15, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

20. The method of claim 15, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,846,648 B2
APPLICATION NO. : 14/099545
DATED : September 30, 2014
INVENTOR(S) : Brian A. Bernick et al.

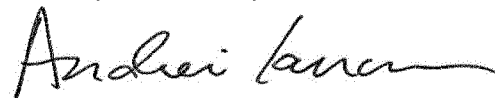
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,846,648 B2
APPLICATION NO. : 14/099545
DATED : September 30, 2014
INVENTOR(S) : Brian A. Bernick et al.

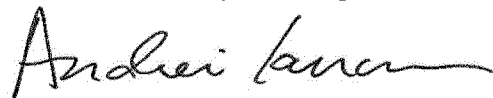
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 24, Claim 15, Line 16: Delete “agnt” and insert in its place --agent--.

Signed and Sealed this
Twentieth Day of August, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu", written in a cursive style.

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT C



US008846649B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 8,846,649 B2**
(45) **Date of Patent:** ***Sep. 30, 2014**

(54) **NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
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(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are pro-
vided herein. Among others, the following formulations are
provided herein: solubilized estradiol without progesterone;
micronized progesterone without estradiol; micronized
progesterone with partially solubilized progesterone; solubi-
lized estradiol with micronized progesterone; solubilized
estradiol with micronized progesterone in combination with
partially solubilized progesterone; and solubilized estradiol
with solubilized progesterone.

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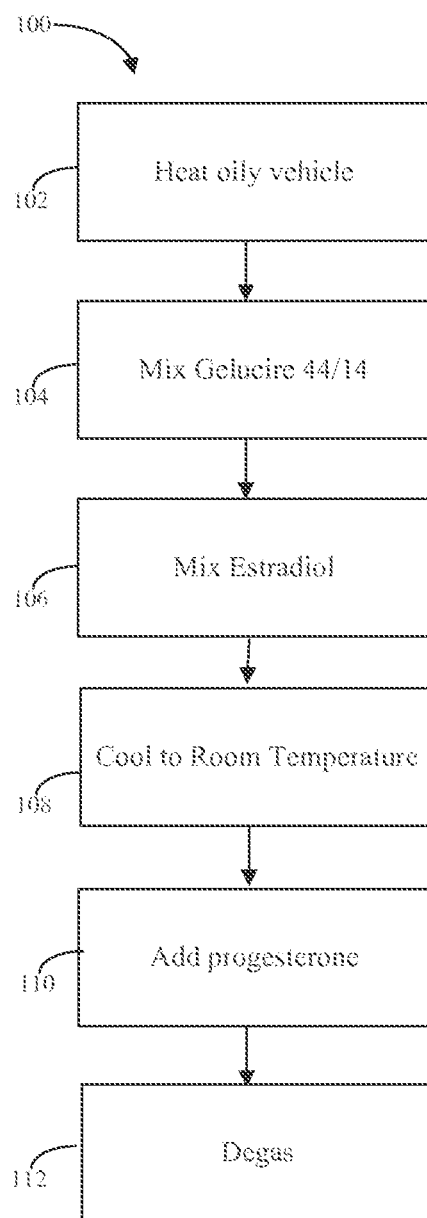


Fig. 1

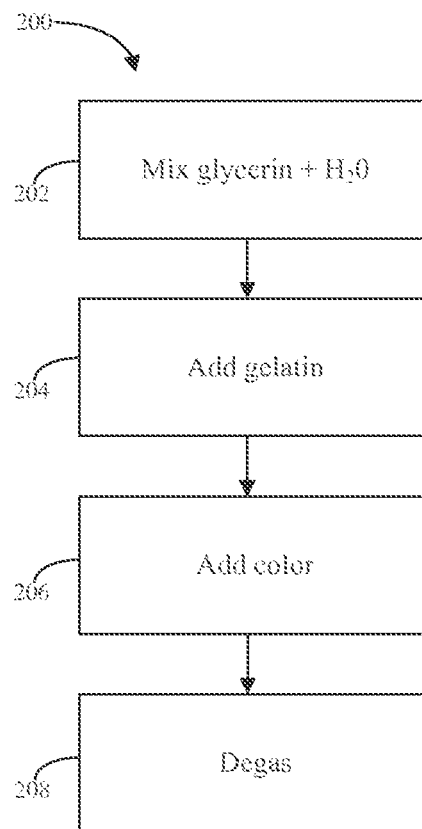


Fig. 2

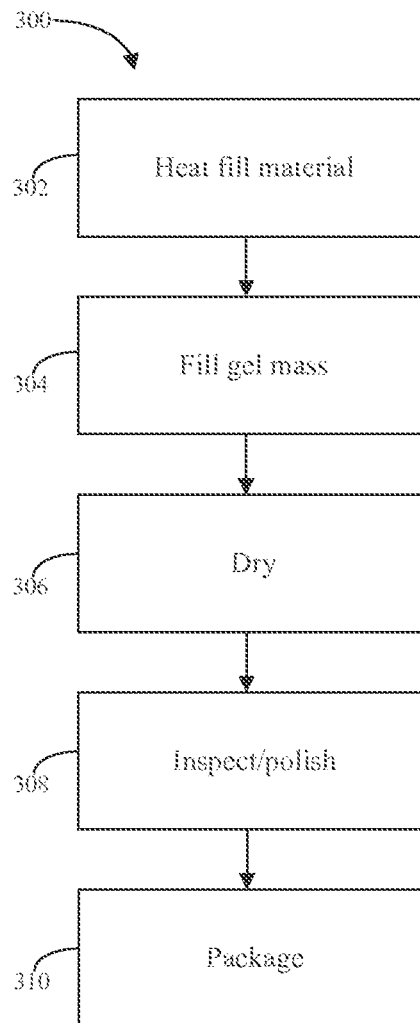


Fig. 3

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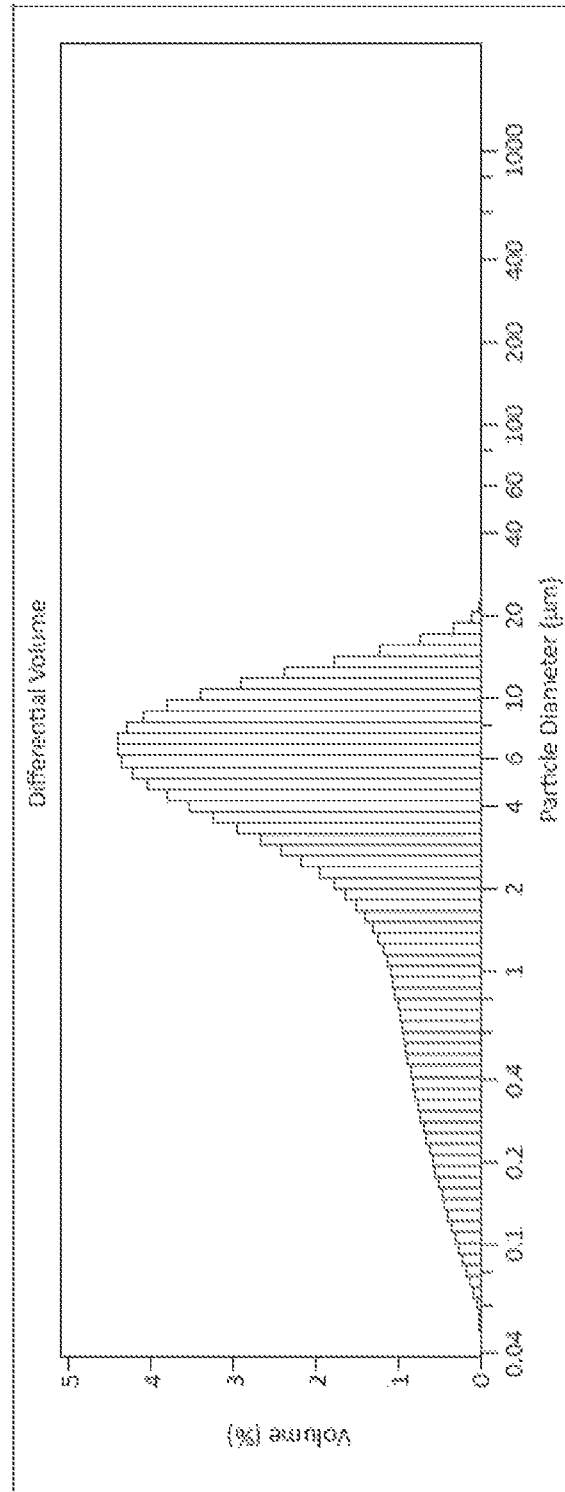


FIG. 4

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1

NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a non-provisional application of and claims priority to the following U.S. Provisional patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

2

"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as PREM-PRO (conjugated estrogens/medroxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens plus medroxyprogesterone acetate tablets) (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN (conjugated estrogens tablets) (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

DEFINITIONS

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to PROMETRIUM (progesterone, USP) at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, T_{max} .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ C_{max} ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ T_{max} ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to estab-

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lished governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

DESCRIPTION

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM (progesterone, USP) when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg:50 mg to about 2 mg:1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

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Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of PROMETRIUM (progesterone, USP). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM (progesterone, USP) at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM (progesterone, USP) can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/

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sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μ m to 2000 μ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These

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formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE (a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride); SASOL Germany GMBH, Hamburg; MIGLYOL (caprylic/capric triglyceride) includes MIGLYOL 810 (Caprylic/Capric Triglyceride), MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 816 (Caprylic/Capric Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL PG-10 (Propylene Glycol Monocaprate); the CAPMUL brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM (Medium Chain Mono- and Diglycerides)); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL (diethylene glycol mono ester)); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL (caprylic/capric triglyceride); TRANSCUTOL (Diethylene glycol monoethyl ether), MIGLYOL (caprylic/capric triglyceride) and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant; and CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for full solubilization of progesterone. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride) can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

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Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxy-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may

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comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from errone-

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ous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF)	141
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	31.2

*Literature reference - Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) at 50%; and also CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL PG-8 (Propylene Glycol Monocaprylate) mixed with MIGLYOL (caprylic/capric triglyceride) at the 15 and 30% level did not provide sufficient solubility.

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TABLE 2

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (85:15)	4.40
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	8.60
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	>12
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	>12
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	14.0
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	19.8
Polysorbate 80:CAPMUL MCM (Medium Chain Mono- and Diglycerides) (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. MIGLYOL 812 (Caprylic/Capric Triglyceride) with 4% TRANSCUTOL (Diethylene glycol monoethyl ether) precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL (caprylic/capric triglyceride): CAPMUL (a propylene glycol monocaprylate; propylene glycol monocaprylate) blends at 30 and 50% or in CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride) (4:96)	4	Crystallizes after 96 hours
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	6	Clear, after 14 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	6	Clear, after 14 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	6	Clear after 14 days

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12 mg estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) 50:50, CAPMUL MCM (Medium Chain Mono- and Diglycerides), and in mixtures of TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Clear, after 12 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization. All CAPMUL PG-8 (Propylene Glycol Monocaprylate) containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL PG-8 (Propylene Glycol Monocaprylate) alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25)	6	Precipitated
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate)	12	Hazy

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TABLE 5-continued

Formulation	Estradiol mg/g	Results after addition of 7% water
Monocaprylate) (50:50)		
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Hazy
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF))	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/ triglycerides of caprylic/capric	322.97	99.38	3.23 kg

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TABLE 8-continued

Ingredient	Mg/Capsule	% w/w	Amount/Batch
acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))			
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL (caprylic/capric triglyceride) was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL (caprylic/capric triglyceride) may be used in embodiments comprising a suspension of progesterone, though MIGLYOL (caprylic/capric triglyceride), standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM (Medium Chain Mono- and Diglycerides) is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL (caprylic/capric triglyceride) had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL MCM (Medium Chain Mono- and Diglycerides). It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL MCM (Medium Chain Mono- and Diglycerides).

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	73.4
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	95
MIGLYOL 812 (Caprylic/ Capric Triglyceride)	27.8

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In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM (Medium Chain Mono- and Diglycerides) in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Gelucire 44/14 system, wherein the ratio of CAPMUL MCM (Medium Chain Mono- and Diglycerides) to GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (9:1)	86.4
CAPMUL MCM (Medium Chain Mono- and Diglycerides) GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (7:3)	70.5
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (6:4)	57.4

Example 7

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97
GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL MCM (Medium Chain Mono- and Diglycerides) may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to

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40° C. +/-2° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) may be added to the CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Heat may be removed from the GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/ Capric Triglyceride) or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/ Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL (caprylic/capric triglyceride) is heated to about 45° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/ diglycerides/ triglycerides of caprylic/capric acid	394.0	65.67	Carrier	3.94

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TABLE 13-continued

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
(CAPMUL MCM (Medium Chain Mono- and Diglycerides)) Lauroyl polyoxyl-32- glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to about 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/ Capric Triglyceride) or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL (caprylic/capric triglyceride) may be present in a range from about 35-95% by weight; GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10

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mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μ m, an X75 of 7.442 μ m, and an X25 of 1.590 μ m. The Beckman Device also yielded that the mean particle size is 4.975 μ m, the median particle size is 4.279 μ m, the mode particle size is 6.453 μ m, and the standard deviation is 3.956 μ m. A graph of the particle distribution obtained is shown in FIG. 4.

Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μ m, an X75 of 17.3 μ m, and an X25 of 5.3 μ m. The Beckman Device also yielded that the mean particle size is 11.8 μ m, the median particle size is 11.04 μ m, the mode particle size is 13.6 μ m, and the standard deviation is 7.8 μ m.

Example 12

In order to increase the solubility of progesterone in the final solution, GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97	5.78
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 40° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

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TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL MCM (Medium Chain Mono-and Diglycerides), NF		73.371	146.74	1467.42
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.500	3.00	30.00
Total:			100.000	200.00 mg	2000.00

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	CAPMUL MCM (Medium Chain Mono-and Diglycerides), NF		65.32	391.93	3919.3
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The

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mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM (progesterone, USP) (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM (progesterone, USP) soft gel Capsule 200 mg and ESTRACE (estradiol vaginal cream, USP, 0.01%) (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient tem-

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perature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of $-70^{\circ}\text{C} \pm 20^{\circ}\text{C}$ in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to $40^{\circ}\text{C} \pm 5^{\circ}\text{C}$. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 .

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

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With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Heating may be performed until the temperature reaches $80^{\circ}\text{C} \pm 5^{\circ}\text{C}$.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to $30^{\circ}\text{C} \pm 3^{\circ}\text{C}$. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes. Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of $55^{\circ}\text{C} \pm 10^{\circ}\text{C}$. The wedge temperature may be $38^{\circ}\text{C} \pm 3^{\circ}\text{C}$. The drum cooling temperature may be $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$. The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness $0.85\text{ mm} \pm 0.05\text{ mm}$ using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight $\pm 5\%$ (i.e., $650 \pm 33\text{ mg}$ and $325 \pm 16.3\text{ mg}$).

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of $55^{\circ}\text{C} \pm 10^{\circ}\text{C}$. The wedge temperature may be $38^{\circ}\text{C} \pm 3^{\circ}\text{C}$. The drum cooling temperature may be $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness $0.85\text{ mm} \pm 0.05\text{ mm}$ using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight $\pm 5\%$ (i.e., $650 \pm 33\text{ mg}$ and $325 \pm 16.3\text{ mg}$).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl

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alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A pharmaceutical composition comprising:
solubilized estradiol;
suspended progesterone;
and a solubilizing agent;
wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;
wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and
wherein the solubilizing agent comprises an effective amount of at least one of mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid.

2. The pharmaceutical composition of claim 1, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

3. The pharmaceutical composition of claim 1, wherein the formulation is formulated as a gelatin capsule.

4. The pharmaceutical composition of claim 1, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

5. The pharmaceutical composition of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

6. A pharmaceutical composition comprising:
solubilized estradiol;
suspended progesterone; and
a solubilizing agent, the solubilizing agent comprising an effective amount of mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid;
wherein the estradiol and the suspended progesterone are present in the solubilizing agent the estradiol and progesterone are uniformly dispersed, and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

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wherein the estradiol does not precipitate for at least 14 days.

7. The pharmaceutical composition of claim 6, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

8. The pharmaceutical composition of claim 6, wherein the composition is formulated as a gelatin capsule.

9. The pharmaceutical composition of claim 6, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

10. The pharmaceutical composition of claim 6, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

11. A method of treating menopause symptoms of a woman with a uterus comprising:

administering an effective amount of a pharmaceutical composition, the pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent,

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises an effective amount of at least one of mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid.

12. The method of claim 11, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

13. The method of claim 11, wherein the composition is formulated in a gelatin capsule.

14. The method of claim 11, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

15. The method of claim 11, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,846,649 B2
APPLICATION NO. : 14/099571
DATED : September 30, 2014
INVENTOR(S) : Brian A. Bernick et al.

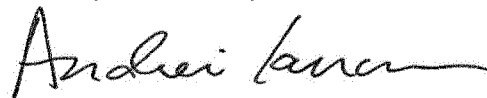
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT D



US008987237B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 8,987,237 B2**
(45) **Date of Patent:** ***Mar. 24, 2015**

(54) **NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

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(2013.01); **A61K 31/565** (2013.01); **A61K**
31/57 (2013.01); **A61K 9/4858** (2013.01)

USPC **514/169**; 424/452

(58) **Field of Classification Search**

CPC **A61K 31/56**
See application file for complete search history.

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Primary Examiner — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend &
Stockton LLP

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are pro-
vided herein. Among others, the following formulations are
provided herein: solubilized estradiol without progesterone;
micronized progesterone without estradiol; micronized
progesterone with partially solubilized progesterone; solubi-
lized estradiol with micronized progesterone; solubilized
estradiol with micronized progesterone in combination with
partially solubilized progesterone; and solubilized estradiol
with solubilized progesterone.

20 Claims, 4 Drawing Sheets

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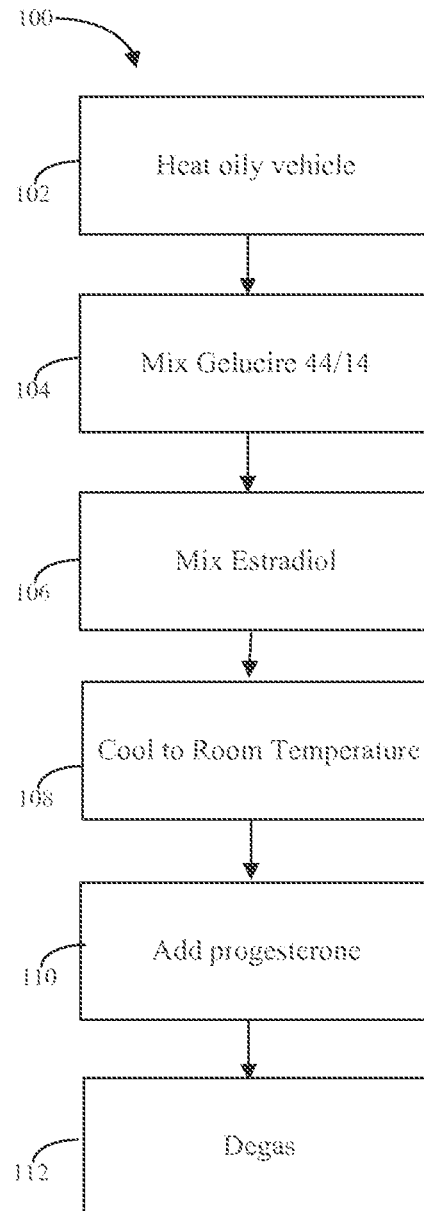


Fig. 1

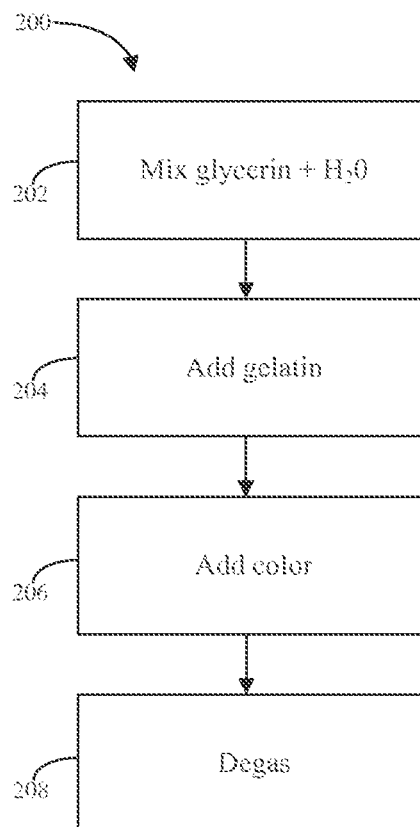


Fig. 2

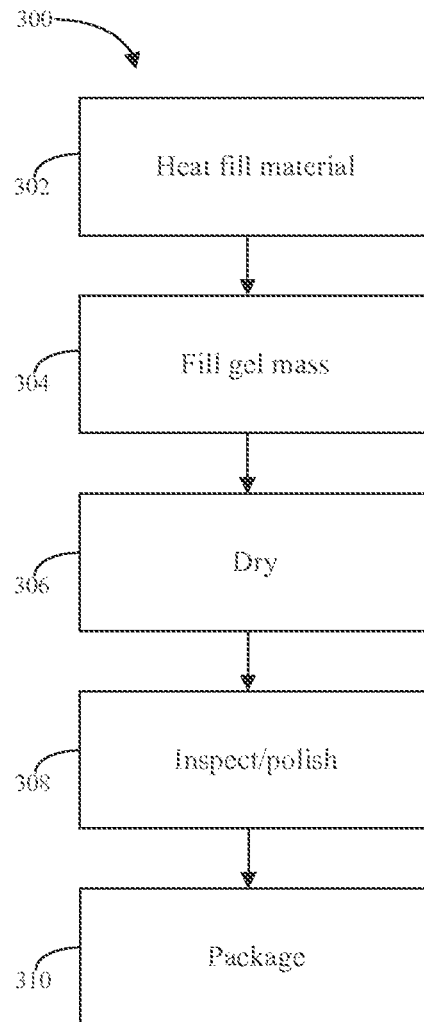


Fig. 3

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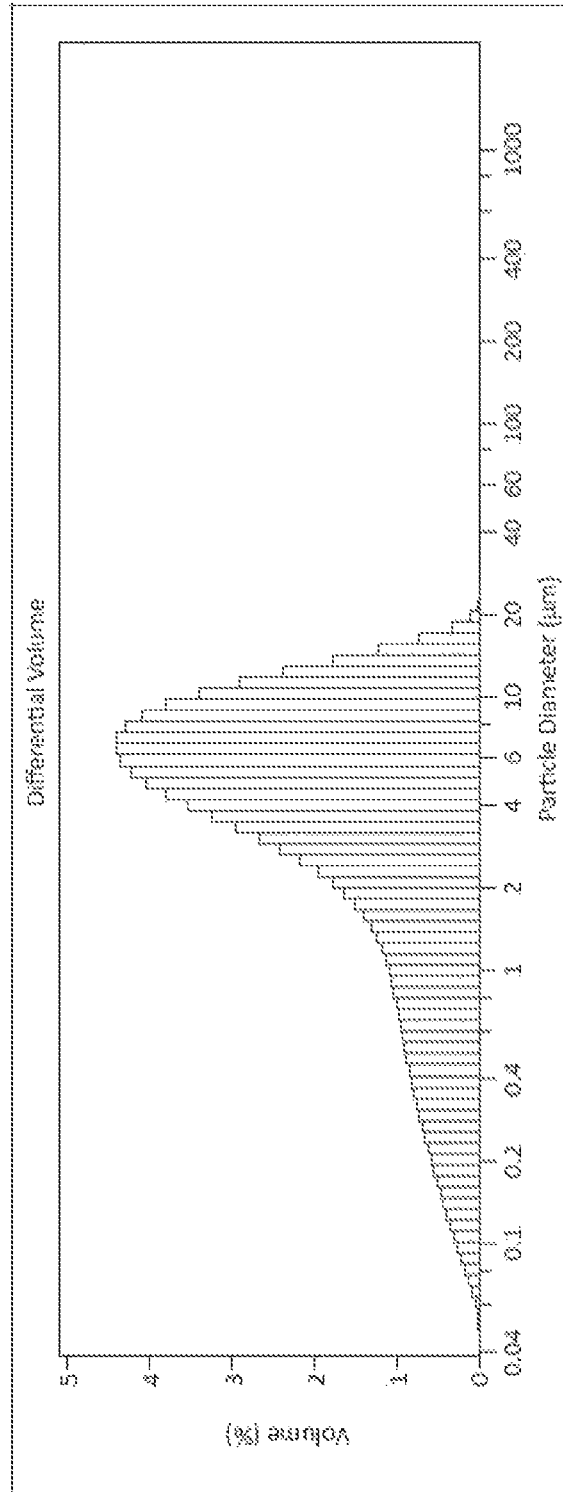


FIG. 4

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NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a non-provisional application of and claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

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"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as PREM-PRO (conjugated estrogens/medroxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens plus medroxyprogesterone acetate tablets) (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN (conjugated estrogens tablets) (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

DEFINITIONS

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to PROMETRIUM (progesterone, USP) at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, T_{max} .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ C_{max} ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ T_{max} ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to estab-

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lished governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

DESCRIPTION

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM (progesterone, USP) when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg:50 mg to about 2 mg:1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

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Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of PROMETRIUM (progesterone, USP). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM (progesterone, USP) at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM (progesterone, USP) can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/

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sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μ m to 2000 μ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These

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formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE (a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride); SASOL Germany GMBH, Hamburg; MIGLYOL (caprylic/capric triglyceride) includes MIGLYOL 810 (Caprylic/Capric Triglyceride), MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 816 (Caprylic/Capric Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL PG-10 (Propylene Glycol Monocaprate); the CAPMUL brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM (Medium Chain Mono- and Diglycerides)); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL (diethylene glycol mono ester)); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL (caprylic/capric triglyceride); TRANSCUTOL (Diethylene glycol monoethyl ether), MIGLYOL (caprylic/capric triglyceride) and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant; and CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for full solubilization of progesterone. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride) can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

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Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxy-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may

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comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from errone-

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ous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF)	141
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	31.2

*Literature reference -Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) at 50%; and also CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL PG-8 (Propylene Glycol Monocaprylate) mixed with MIGLYOL (caprylic/capric triglyceride) at the 15 and 30% level did not provide sufficient solubility.

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TABLE 2

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (85:15)	4.40
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	8.60
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	>12
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	>12
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	14.0
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	19.8
Polysorbate 80:CAPMUL MCM (Medium Chain Mono- and Diglycerides) (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. MIGLYOL 812 (Caprylic/Capric Triglyceride) with 4% TRANSCUTOL (Diethylene glycol monoethyl ether) precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL (a propylene glycol monocaprylate; propylene glycol monocaprylate) blends at 30 and 50% or in CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride) (4:96)	4	Crystallizes after 96 hours
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	6	Clear, after 14 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	6	Clear, after 14 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	6	Clear after 14 days

12 mg estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) 50:50, CAPMUL MCM(Medium Chain Mono- and Diglycerides), and in mixtures of TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) are stable and do not precipitate for at least 12 days.

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TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Clear, after 12 days
CAPMUL MCM(Medium Chain Mono- and Diglycerides)	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization. All CAPMUL PG-8 (Propylene Glycol Monocaprylate) containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL PG-8 (Propylene Glycol Monocaprylate) alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25)	6	Precipitated
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Hazy
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Hazy
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear

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TABLE 5-continued

Formulation	Estradiol mg/g	Results after addition of 7% water
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (TRANSCUTOL IHP (Highly purified diethylene glycol monoethyl ether EP/NF))	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved.

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Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL (caprylic/capric triglyceride) was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL (caprylic/capric triglyceride) may be used in embodiments comprising a suspension of progesterone, though MIGLYOL (caprylic/capric triglyceride), standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM (Medium Chain Mono- and Diglycerides) is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL (caprylic/capric triglyceride) had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL MCM (Medium Chain Mono- and Diglycerides). It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL MCM (Medium Chain Mono- and Diglycerides).

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	73.4
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	95
MIGLYOL 812 (Caprylic/ Capric Triglyceride)	27.8

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM (Medium Chain Mono- and Diglycerides) in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Gelucire 44/14 system, wherein the ratio of CAPMUL MCM (Medium Chain Mono- and Diglycerides) to GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is 9:1.

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TABLE 10

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (9:1)	86.4
CAPMUL MCM (Medium Chain Mono- and Diglycerides) GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (7:3)	70.5
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (6:4)	57.4

Example 7

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97
GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL MCM (Medium Chain Mono- and Diglycerides) may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/-2° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) may be added to the CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Heat may be removed from the GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) and CAPMUL MCM (Medium Chain Mono- and Diglycerides)

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mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL (caprylic/capric triglyceride) is heated to about 45° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2%

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w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to about 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL (caprylic/capric triglyceride) may be present in a range from about 35-95% by weight; GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μ m, an X75 of 7.442 μ m, and an X25 of 1.590 μ m. The Beckman Device also yielded that the mean particle size is 4.975 μ m, the median particle size is 4.279 μ m, the mode particle size is 6.453 μ m, and the standard deviation is 3.956 μ m. A graph of the particle distribution obtained is shown in FIG. 4.

Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μ m, an X75 of 17.3 μ m, and an X25 of 5.3 μ m. The Beckman Device also yielded that the mean particle size is 11.8 μ m, the median

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particle size is 11.04 μ m, the mode particle size is 13.6 μ m, and the standard deviation is 7.8 μ m.

Example 12

In order to increase the solubility of progesterone in the final solution, GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97	5.78
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 40° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		73.371	146.74	1467.42
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF		1.500	3.00	30.00

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TABLE 16-continued

Item No.	Ingredient(s)	Label Claim (mg)	Qty/ Capsule (mg)	Amount/ Batch (g)
	Lauroyl polyoxylglycerides (USA FDA IIG)), NF			
Total:		100.000	200.00 mg	2000.00

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		65.32	391.93	3919.3
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.00	6.0	60.0
Total:		100.00	600.0 mg		6000.0

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

Progesterone and Estradiol Combination Study Under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM (progesterone, USP) (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

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The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM (progesterone, USP) soft gel Capsule 200 mg and ESTRACE (estradiol vaginal cream, USP, 0.01%) (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

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At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of $-70^{\circ}\text{C} \pm 20^{\circ}\text{C}$ in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to $40^{\circ}\text{C} \pm 5^{\circ}\text{C}$. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 .

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Heating may be performed until the temperature reaches $80^{\circ}\text{C} \pm 5^{\circ}\text{C}$.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 208 comprises degassing. The

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resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to $30^{\circ}\text{C} \pm 3^{\circ}\text{C}$. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes. Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of $55^{\circ}\text{C} \pm 10^{\circ}\text{C}$. The wedge temperature may be $38^{\circ}\text{C} \pm 3^{\circ}\text{C}$. The drum cooling temperature may be $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$. The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness $0.85\text{ mm} \pm 0.05\text{ mm}$ using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight $\pm 5\%$ (i.e., $650 \pm 33\text{ mg}$ and $325 \pm 16.3\text{ mg}$).

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of $55^{\circ}\text{C} \pm 10^{\circ}\text{C}$. The wedge temperature may be $38^{\circ}\text{C} \pm 3^{\circ}\text{C}$. The drum cooling temperature may be $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness $0.85\text{ mm} \pm 0.05\text{ mm}$ using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight $\pm 5\%$ (i.e., $650 \pm 33\text{ mg}$ and $325 \pm 16.3\text{ mg}$).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A pharmaceutical composition comprising: a solubilizing agent comprising: mono- and diglycerides of capric and caprylic acid; and at least one of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, or lauroyl polyoxyglycerides; progesterone; and estradiol, the estradiol being at least about 90% solubilized in the solubilizing agent; wherein the estradiol and the progesterone are present in the solubilizing agent, and the estradiol and suspended progesterone are uniformly dispersed.

2. The pharmaceutical composition of claim 1, wherein the ratio of progesterone to estradiol is from about 24:1 to about 200:1.

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3. The pharmaceutical composition of claim 2, wherein the ratio of progesterone to estradiol comprises one of: about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, and about 200:1.

4. The pharmaceutical composition of claim 1, wherein the progesterone is between about 7.14% w/w and about 33.33% w/w of the pharmaceutical composition.

5. The pharmaceutical composition of claim 1, wherein the estradiol is between about 0.12% w/w and about 0.35% w/w of the pharmaceutical composition.

6. The pharmaceutical composition of claim 1, wherein the composition is encapsulated in a gelatin capsule; and wherein each gelatin capsule comprises from about 25 mg to about 200 mg of progesterone and from about 0.125 mg to about 2.00 mg of estradiol.

7. The pharmaceutical composition of claim 1, wherein the estradiol is at least 90% solubilized in the solubilizing agent.

8. A pharmaceutical composition comprising:

a solubilizing agent comprising:

monoglycerides and diglycerides of caprylic and capric acid; and

a polyethylene glycol glyceride;

progesterone; and

estradiol, the estradiol being at least about 90% solubilized in the solubilizing agent;

wherein the estradiol and the progesterone are present in the solubilizing agent, and the estradiol and progesterone are uniformly dispersed.

9. The pharmaceutical composition of claim 8, wherein the ratio of progesterone to estradiol is from about 24:1 to about 200:1.

10. The pharmaceutical composition of claim 9, wherein the ratio of progesterone to estradiol comprises one of: about 24:1, about 25:1, about 96:1, about 100:1, about 192:1 and about 200:1.

11. The pharmaceutical composition of claim 8, wherein the progesterone is between about 7.14% w/w and about 33.33% w/w of the pharmaceutical composition.

12. The pharmaceutical composition of claim 8, wherein the estradiol is between about 0.12% w/w and about 0.35% w/w of the pharmaceutical composition.

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13. The pharmaceutical composition of claim 8, wherein the composition is encapsulated in a gelatin capsule; and wherein each gelatin capsule comprises from about 25 mg to about 200 mg of progesterone and from about 0.125 mg to about 2.00 mg of estradiol.

14. The pharmaceutical composition of claim 8, wherein the estradiol is at least 90% solubilized in the solubilizing agent.

15. A pharmaceutical composition comprising:

a solubilizing agent comprising:

mono- and diglycerides of capric and caprylic acid; and at least one of lauroyl macrogol-32 glycerides, lauroyl polyoxyl-32 glycerides, and lauroyl polyoxylglycerides;

progesterone; and

estradiol, the estradiol being at least about 90% solubilized in the solubilizing agent;

wherein the estradiol and the suspended progesterone are present in the solubilizing agent, and the estradiol and suspended progesterone are uniformly.

16. The pharmaceutical composition of claim 15, wherein the ratio of progesterone to estradiol is from about 24:1 to about 200:1.

17. The pharmaceutical composition of claim 15, wherein the ratio of progesterone to estradiol comprises one of: about 24:1, about 25:1, about 96:1, about 100:1, about 192:1 and about 200:1.

18. The pharmaceutical composition of claim 15, wherein the progesterone is between about 7.14% w/w and about 33.33% w/w of the pharmaceutical composition.

19. The pharmaceutical composition of claim 15, wherein the estradiol is between about 0.12% w/w and about 0.35% w/w of the pharmaceutical composition.

20. The pharmaceutical composition of claim 15, wherein the composition is encapsulated in a gelatin capsule; and wherein each gelatin capsule comprises from about 25 mg to about 200 mg of progesterone and from about 0.125 mg to about 2.00 mg of estradiol.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,987,237 B2
APPLICATION NO. : 14/099562
DATED : March 24, 2015
INVENTOR(S) : Brian A. Bernick et al.

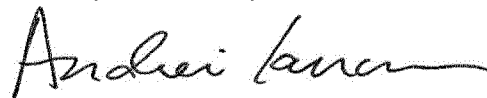
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,987,237 B2
APPLICATION NO. : 14/099562
DATED : March 24, 2015
INVENTOR(S) : Brian A. Bernick et al.

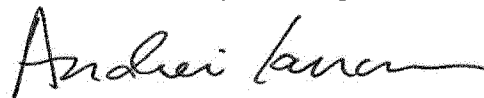
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 24, Claim 15, Line 21: Insert --dispersed-- after “uniformly”.

Signed and Sealed this
Twentieth Day of August, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu", written in a cursive style.

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT E



US008993548B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 8,993,548 B2**
(45) **Date of Patent:** ***Mar. 31, 2015**

(54) **NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

(56) **References Cited**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/475,814**

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Related U.S. Application Data

(60) Continuation of application No. 14/099,545, filed on Dec. 6, 2013, now Pat. No. 8,846,648, which is a division of application No. 13/684,002, filed on Nov. 21, 2012, now Pat. No. 8,633,178.

(60) Provisional application No. 61/662,265, filed on Jun. 20, 2012, provisional application No. 61/661,302, filed on Jun. 18, 2012, provisional application No. 61/563,408, filed on Nov. 23, 2011.

(51) **Int. Cl.**

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A61K 31/565 (2006.01)
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CPC . **A61K 31/57** (2013.01); **A61K 9/16** (2013.01);
A61K 31/565 (2013.01); **A61K 9/4858**
(2013.01); **A61K 9/7023** (2013.01)

USPC **514/169**; 424/452

(58) **Field of Classification Search**

CPC **A61K 31/57**; **A61K 31/565**
USPC **514/169**; 424/452
See application file for complete search history.

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Primary Examiner — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton LLP

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

6 Claims, 4 Drawing Sheets

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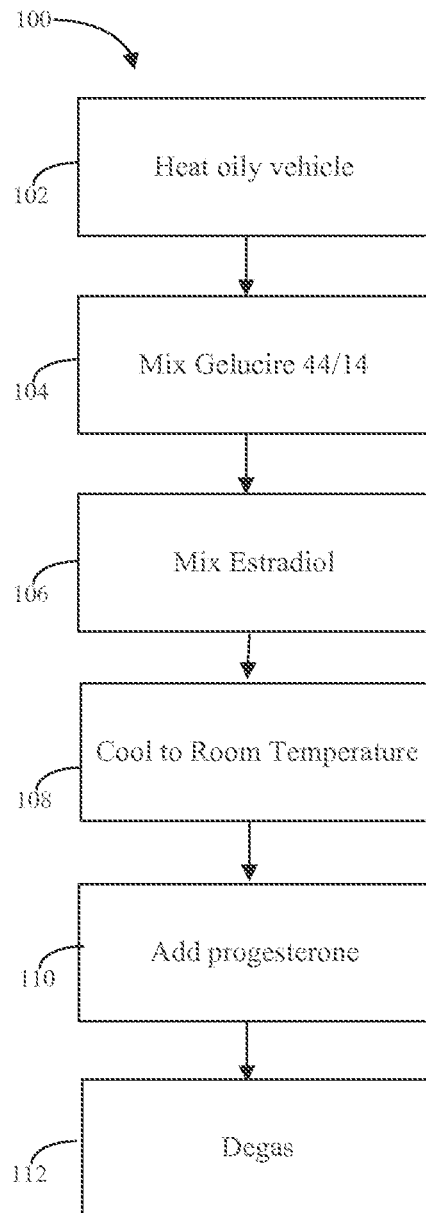


Fig. 1

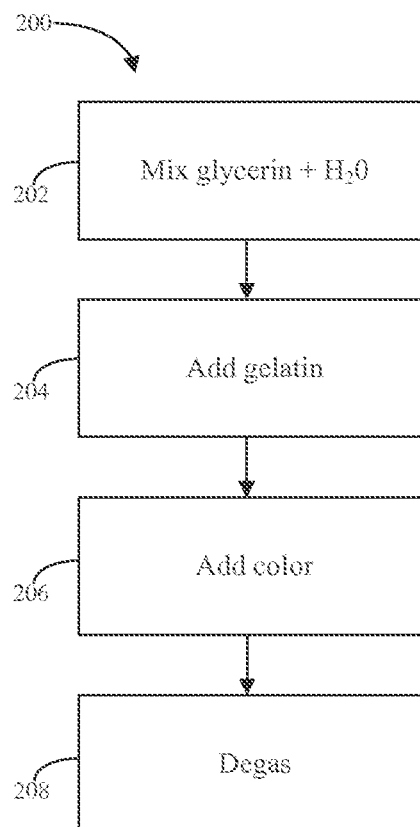


Fig. 2

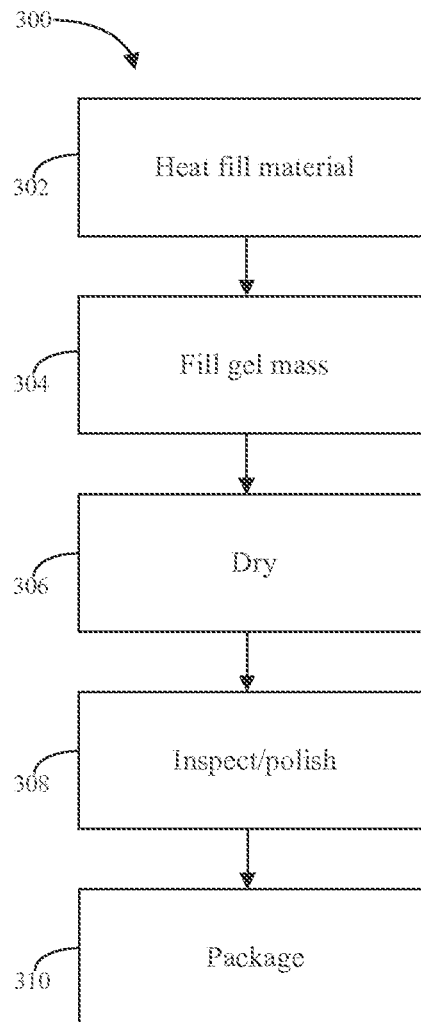


Fig. 3

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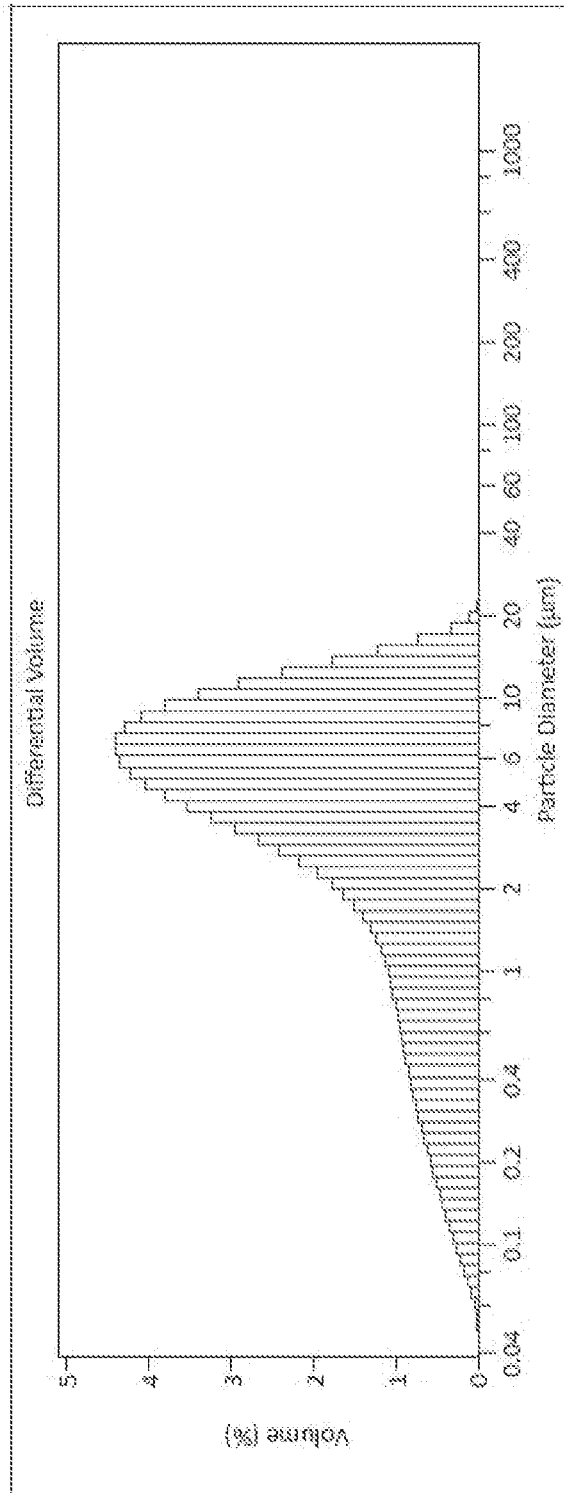


FIG. 4

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NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/099,545, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Dec. 6, 2013, which application is a divisional of U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which application claims priority to the following U.S. Provisional patent applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a

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constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

5 Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

10 "Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

15 These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

20 Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY OF THE INVENTION

25 According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

30 The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

60 FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

65 FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

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DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

A. Definitions

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, T_{max} .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ C_{max} ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ T_{max} ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating

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pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

B. Description and Preferred Embodiments

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra-

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and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125,

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1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μ m to 2000 μ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

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Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GmbH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol; Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Campul MCM; Capmul MCM and a non-ionic surfactant; and Campul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Campul MCM and Gelucire can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other

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solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2, 3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may

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contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and

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filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference—Salole, E.G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

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TABLE 3

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol:Miglyol:Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

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Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/ triglycerides of caprylic/ capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

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As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

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For example, Campul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/-2° C. Gelucire 44/14 may be added to the Campul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Campul MCM.

Heat may be removed from the Gelucire 44/14 and Campul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Campul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

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Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier

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with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μm , an $\times 75$ of 17.3 μm , and an $\times 25$ of 5.3 μm . The Beckman Device also yielded that the mean particle size is 11.8 μm , the median particle size is 11.04 μm , the mode particle size is 13.6 μm , and the standard deviation is 7.8 μm .

Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

TABLE 14-continued

Ingredient	%	mg/ Capsule	Function
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μm , an $\times 75$ of 7.442 μm , and an $\times 25$ of 1.590 μm . The Beckman Device also yielded that the mean particle size is 4.975 μm , the median particle size is 4.279 μm , the mode particle size is 6.453 μm , and the standard deviation is 3.956 μm . A graph of the particle distribution obtained is shown in FIG. 4.

Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:			100.000	200.00 mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

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TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 16

Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout

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the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA-vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ± 20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ± 5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator,

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or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.±3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of

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FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.±10° C. The wedge temperature may be 38° C.±3° C. The drum cooling temperature may be 4° C.±2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant.

Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A pharmaceutical formulation comprising solubilized estradiol, suspended progesterone, and a medium chain solubilizing agent; wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed; wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and wherein the solubilizing agent comprises an effective amount of a C6-C12 oil.

2. The pharmaceutical formulation of claim 1, further comprising partially solubilized progesterone.

3. The pharmaceutical formulation of claim 1, wherein the formulation is contained within a gelatin capsule.

4. The pharmaceutical formulation of claim 1, wherein the medium chain solubilizing agent is selected from at least one of mono-, di-, and triglycerides and combinations thereof.

5. The pharmaceutical formulation of claim 1, wherein said estradiol has a dosage strength at least about 0.125 mg and wherein said progesterone has a dosage strength at least about 25 mg.

6. The pharmaceutical formulation of claim 1, wherein the ratio of progesterone to estradiol is at least 95:1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,993,548 B2
APPLICATION NO. : 14/475814
DATED : March 31, 2015
INVENTOR(S) : Brian A. Bernick et al.

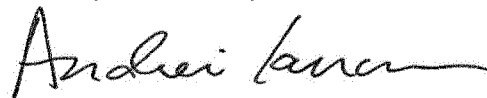
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT F



US008993549B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 8,993,549 B2**
(45) **Date of Patent:** ***Mar. 31, 2015**

(54) **NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

(56) **References Cited**

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patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
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continuation of application No. 13/684,002, filed on
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CPC . **A61K 31/57** (2013.01); **A61K 9/16** (2013.01);
A61K 31/565 (2013.01); **A61K 9/4858**
(2013.01); **A61K 9/7023** (2013.01)
USPC **514/169**; 424/452

(58) **Field of Classification Search**

CPC **A61K 31/57**; **A61K 31/565**
USPC **514/169**; 424/452
See application file for complete search history.

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Primary Examiner — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend &
Stockton LLP

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are pro-
vided herein. Among others, the following formulations are
provided herein: solubilized estradiol without progesterone;
micronized progesterone without estradiol; micronized
progesterone with partially solubilized progesterone; solubi-
lized estradiol with micronized progesterone; solubilized
estradiol with micronized progesterone in combination with
partially solubilized progesterone; and solubilized estradiol
with solubilized progesterone.

18 Claims, 4 Drawing Sheets

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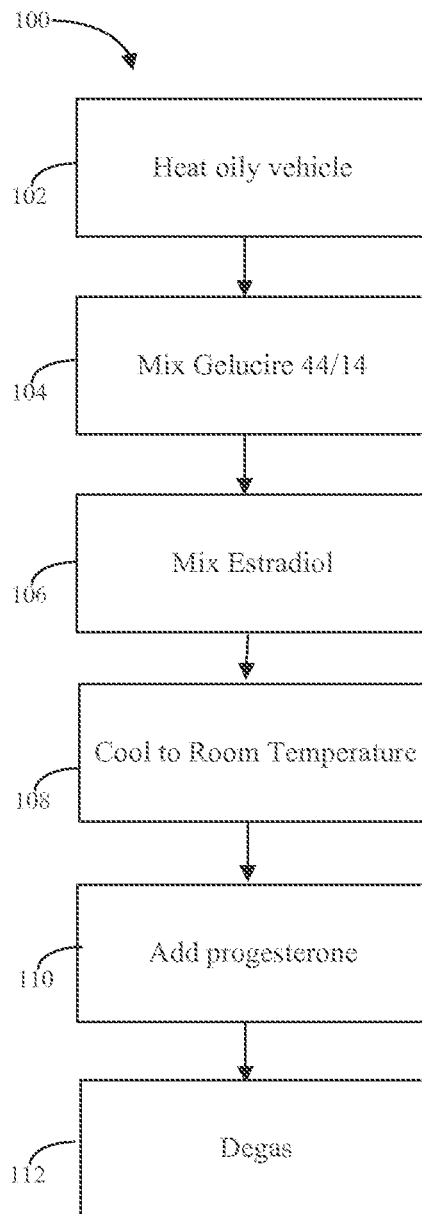


Fig. 1

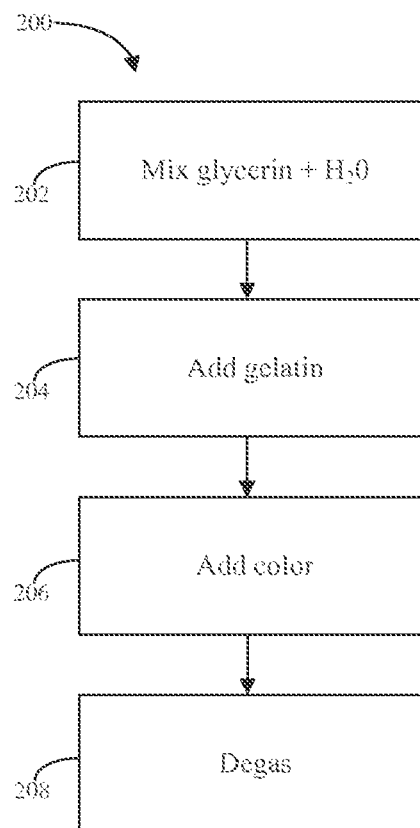


Fig. 2

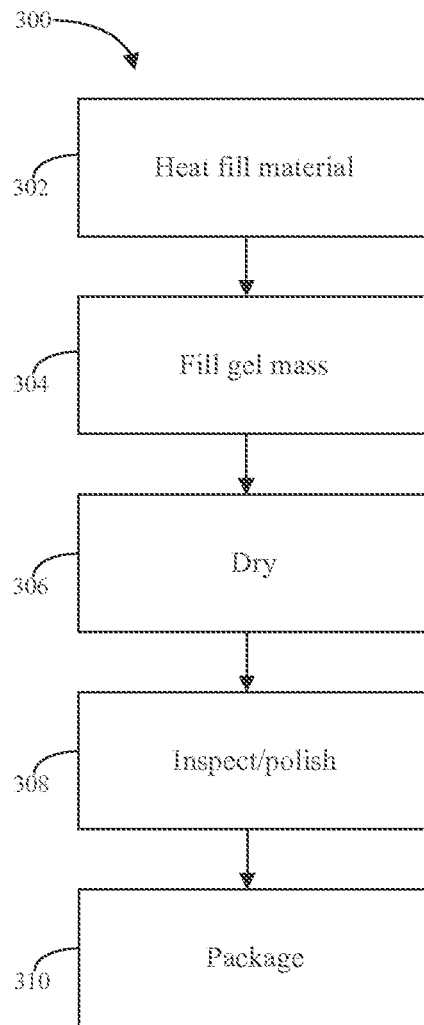


Fig. 3

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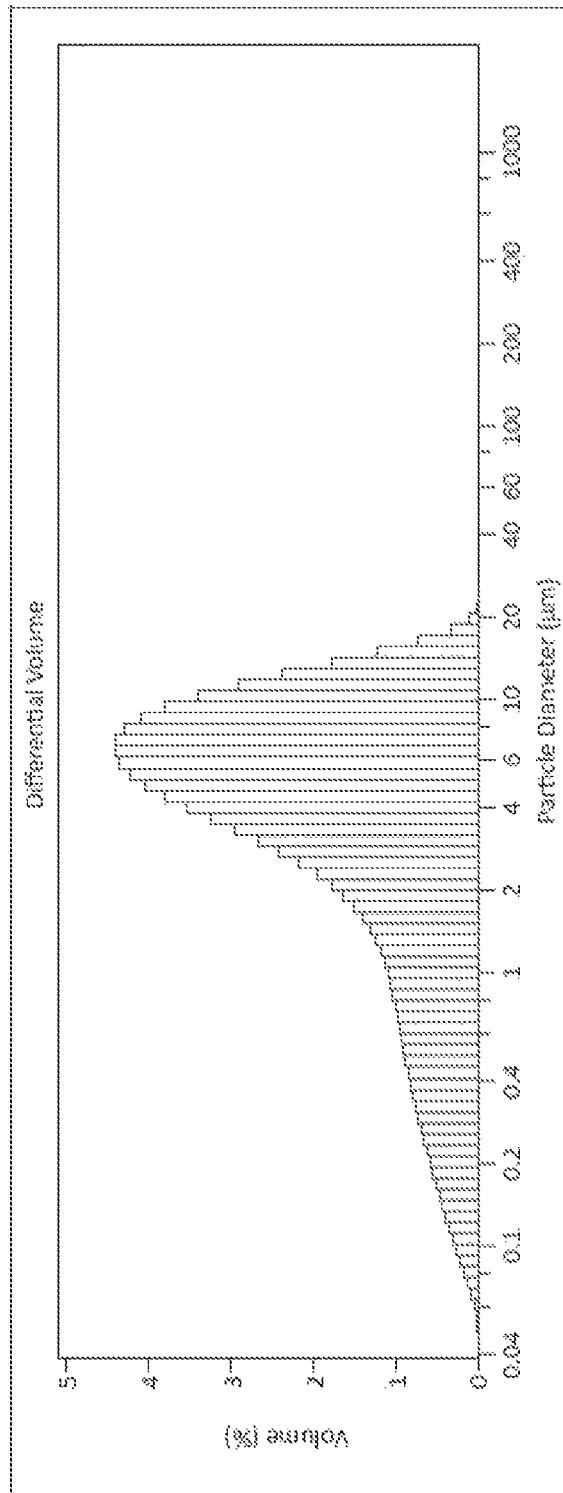


FIG. 4

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NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/099,571, entitled “NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES” which was filed on Dec. 6, 2013, which is a continuation of U.S. patent application Ser. No. 13/684,002, entitled “NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES” which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled “NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES” which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled “ESTRADIOL FORMULATIONS” which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled “PROGESTERONE FORMULATIONS” which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as “Cyclic-Sequential” or “Sequentially-Combined HRT.” This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken

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daily, is called “continuous-combined HRT.” This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

“Bio-identical” hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare’s urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY OF THE INVENTION

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

A. DEFINITIONS

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, T_{max} .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ C_{max} ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ T_{max} ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to estab-

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lished governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

B. DESCRIPTION AND PREFERRED EMBODIMENTS

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg:50 mg to about 2 mg:1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

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Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for

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use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μ m to 2000 μ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be

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combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol; Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Campul MCM; Capmul MCM and a non-ionic surfactant; and Campul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Campul MCM and Gelucire can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

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In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days

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identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g

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solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference—Salole, E.G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

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TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:	6	Clear, after 14 days
Capmul PG8 (5:80:15)		
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol: Miglyol: Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:	12	Clear, after 12 days
Capmul PG8 (5:65:28)		
Transcutol:Miglyol 812:	12	Clear, after 12 days
Capmul PG8 (5:47:47)		
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg

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progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM: Gelucire 44/14 (9:1)	86.4
Capmul MCM: Gelucire 44/14 (7:3)	70.5
Capmul MCM: Gelucire 44/14 (6:4)	57.4

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

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For example, Capmul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/- 2° C. Gelucire 44/14 may be added to the Capmul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Capmul MCM.

Heat may be removed from the Gelucire 44/14 and Capmul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Capmul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

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Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

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Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μm , an X75 of 17.3 μm , and an X25 of 5.3 μm . The Beckman Device also yielded that the mean particle size is 11.8 μm , the median particle size is 11.04 μm , the mode particle size is 13.6 μm , and the standard deviation is 7.8 μm .

Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:			100.000	200.00mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and

Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μm , an X75 of 7.442 μm , and an X25 of 1.590 μm . The Beckman Device also yielded that the mean particle size is 4.975 μm , the median particle size is 4.279 μm , the mode particle size is 6.453 μm , and the standard deviation is 3.956 μm . A graph of the particle distribution obtained is shown in FIG. 4.

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dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:		100.00	600.0 mg	6000.0	

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 16

Progesterone and Estradiol Combination Study
Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the

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study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ±20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel

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vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.±3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.±10° C. The wedge temperature may be 38° C.±3° C. The drum cooling temperature may be 4° C.±2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thick-

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ness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A pharmaceutical composition comprising:

solubilized estradiol;
suspended progesterone; and
a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;
wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises an effective amount of a monoglyceride, a diglyceride or a combination thereof containing an ester of a C6-C12 fatty acid.

2. The pharmaceutical composition of claim 1, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

3. The pharmaceutical composition of claim 1, wherein the formulation is formulated as a gelatin capsule.

4. The pharmaceutical composition of claim 1, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

5. The pharmaceutical composition of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

6. The pharmaceutical composition of claim 1, wherein the estradiol does not precipitate for at least 14 days.

7. A pharmaceutical composition comprising:

solubilized estradiol;
suspended progesterone; and
a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;
wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises an effective amount of a monoglyceride thereof containing an ester of a C6-C12 fatty acid.

8. The pharmaceutical composition of claim 7, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

9. The pharmaceutical composition of claim 7, wherein the composition is formulated as a gelatin capsule.

10. The pharmaceutical composition of claim 7, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

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11. The pharmaceutical composition of claim 7, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

12. The pharmaceutical composition of claim 7, wherein the estradiol does not precipitate for at least 14 days. 5

13. A pharmaceutical composition comprising:

solubilized estradiol;

suspended progesterone; and

a solubilizing agent;

wherein each of the estradiol and the suspended progesterone 10

are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;

wherein at least about 90% of the estradiol is solubilized in

the solubilizing agent; and

wherein the solubilizing agent comprising an effective 15

amount of a diglyceride containing an ester of a C6-C12 fatty acid.

14. The pharmaceutical composition of claim 13, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent. 20

15. The pharmaceutical composition of claim 13, wherein the composition is formulated in a gelatin capsule.

16. The pharmaceutical composition of claim 13, wherein the estradiol has a dosage strength of at least about 0.125 mg 25 and wherein the progesterone has a dosage strength of at least about 25 mg.

17. The pharmaceutical composition of claim 13, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1. 30

18. The pharmaceutical composition of claim 13, wherein the estradiol does not precipitate for at least 14 days.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,993,549 B2
APPLICATION NO. : 14/475864
DATED : March 31, 2015
INVENTOR(S) : Brian A. Bernick et al.

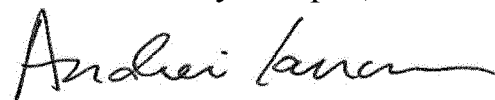
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Second Day of April, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu", written in a cursive style.

Andrei Iancu
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,993,549 B2
APPLICATION NO. : 14/475864
DATED : March 31, 2015
INVENTOR(S) : Brian A. Bernick et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 20, Claim 7, Line 56: Delete “thereof”.

Signed and Sealed this
Thirteenth Day of August, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu", written in a cursive style.

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT G



US009006222B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 9,006,222 B2**
(45) **Date of Patent:** ***Apr. 14, 2015**

(54) **NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
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(51) **Int. Cl.**

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(52) **U.S. Cl.**

CPC **A61K 31/57** (2013.01); **A61K 31/565**
(2013.01); **A61K 47/44** (2013.01); **A61K**
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(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend &
Stockton LLP

(57)

ABSTRACT

Estrogen and progesterone replacement therapies are pro-
vided herein. Among others, the following formulations are
provided herein: solubilized estradiol without progesterone;
micronized progesterone without estradiol; micronized
progesterone with partially solubilized progesterone; solubi-
lized estradiol with micronized progesterone; solubilized
estradiol with micronized progesterone in combination with
partially solubilized progesterone; and solubilized estradiol
with solubilized progesterone.

12 Claims, 5 Drawing Sheets

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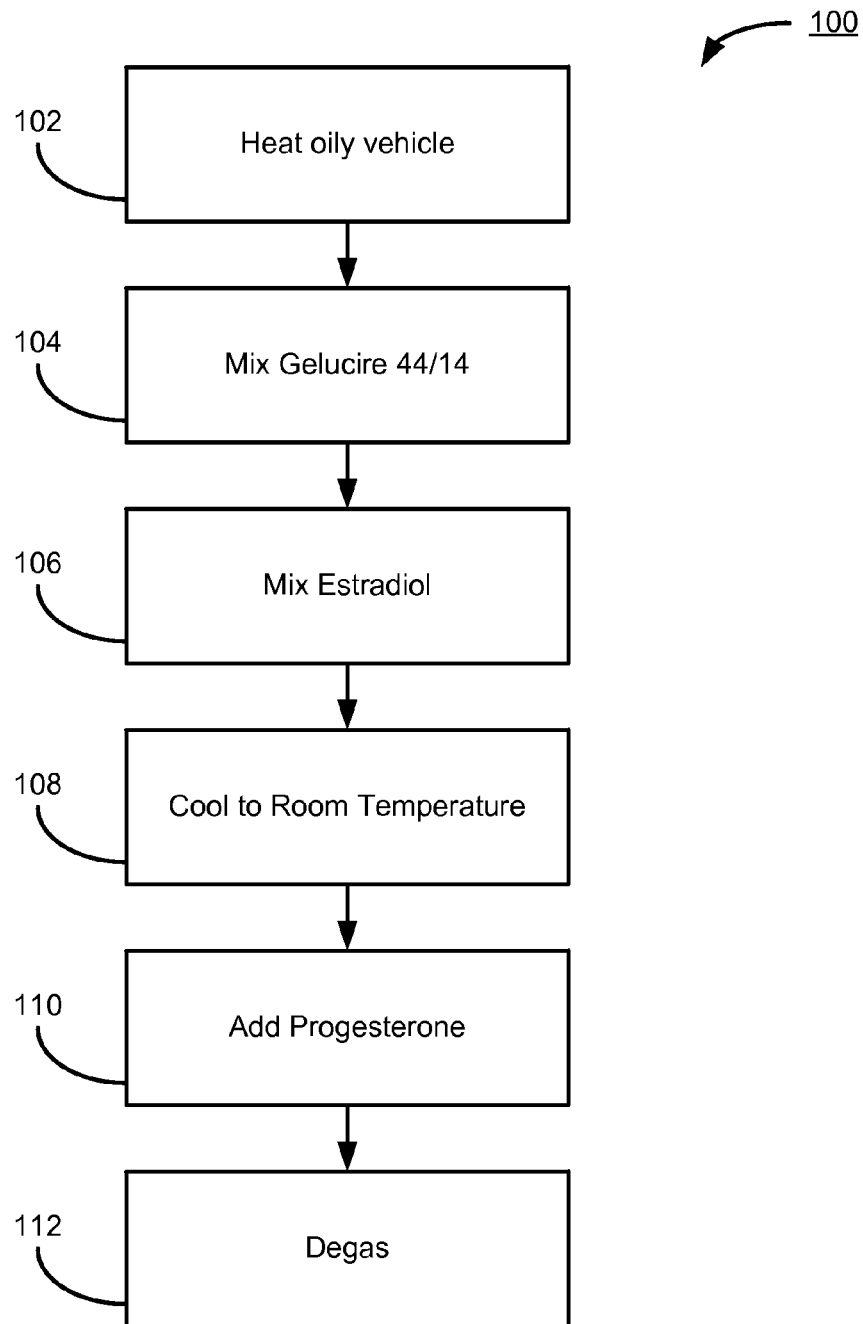


FIG. 1

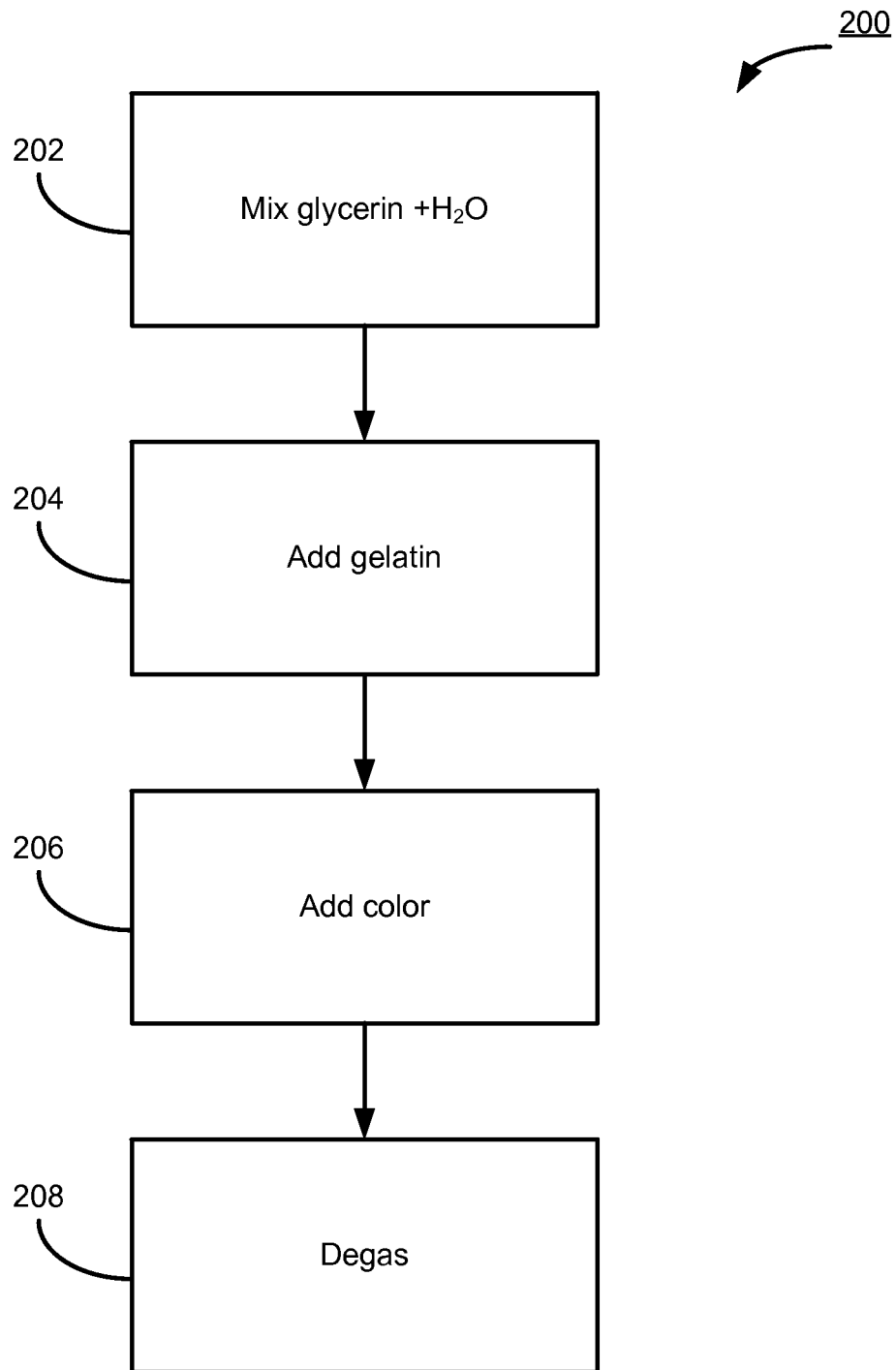


FIG. 2

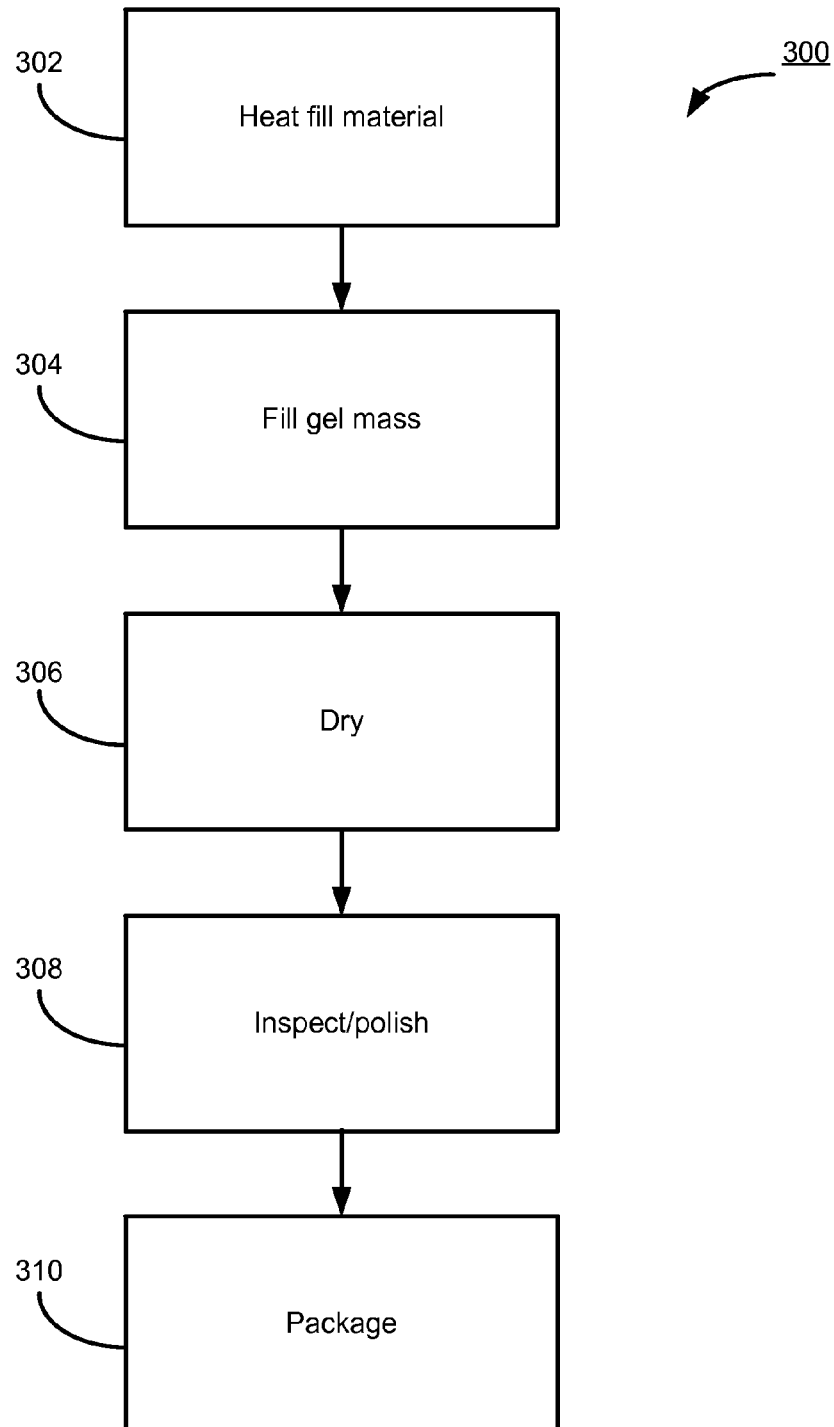


FIG. 3

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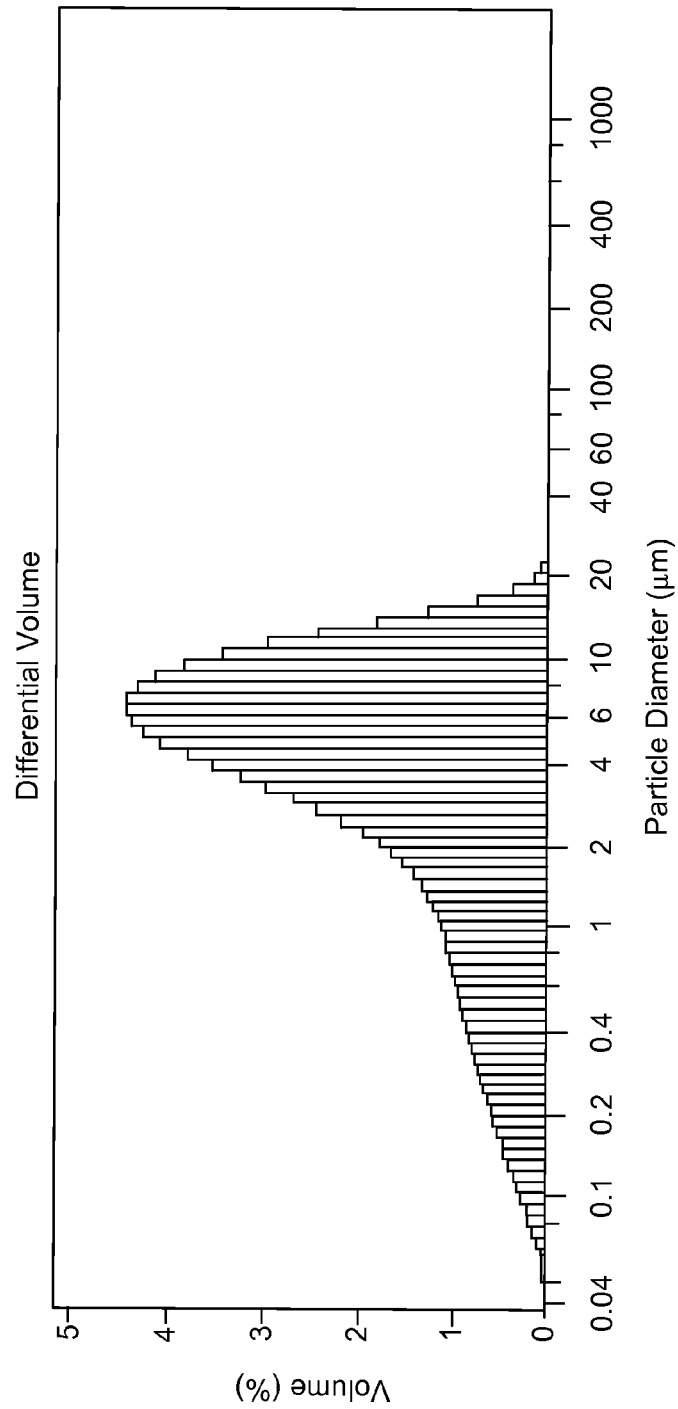


FIG. 4

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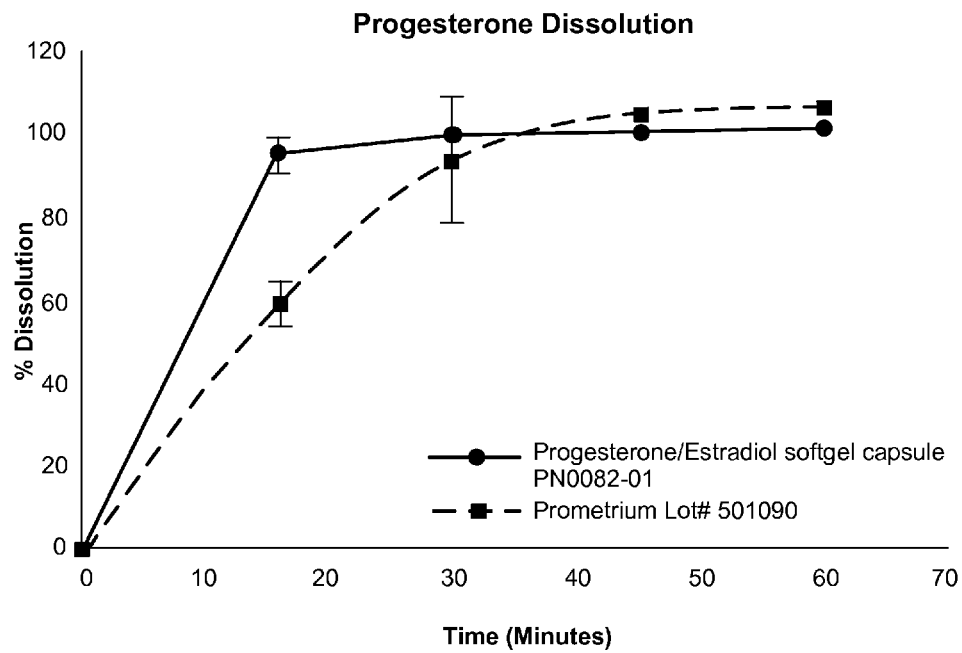


FIG. 5

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1

NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to the following U.S. Patent Applications: U.S. application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES," which was filed on Nov. 21, 2012; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULA- TIONS," which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bod-

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ies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Prometrium was approved for sale in the United States on May 14, 1998 under NDA #N019781. According to the prescribing information approved for this product (Rev June 2009) ("Prometrium prescribing information"), Prometrium comprises synthetic progesterone that is chemically identical to progesterone of human ovarian origin. Capsules comprise 100 mg or 200 mg of micronized progesterone. The inactive ingredients include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, and yellow and red dyes.

Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

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FIG. 5 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

Definitions

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, Cmax, and optionally, Tmax.

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “Cmax” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “Tmax” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, Cmax and, optionally, Tmax are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal especially a mammal, including human, subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without

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limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, such as an organic oil other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution, i.e., at least 98% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%, i.e., up to but not including 98% in solution.

As used herein, unless specified, estradiol includes estradiol in anhydrous and hemihydrate forms.

DESCRIPTION

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be

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desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %; estradiol is 0.1 to 0.8 wt %, e.g., 0.15 to 0.35 wt %.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

According to the Prometrium prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered Prometrium once a day for five days resulted in the mean PK parameters listed in the following table:

Parameter	Prometrium Capsules Daily Dose		
	100 mg	200 mg	300 mg
C_{max} (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
T_{max} (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
AUC_{0-10} (ng x hr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

In a particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions

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treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing

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zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of caproic fatty acid; caprylic fatty acid; capric fatty acid; tauric acid; myristic acid; linoleic acid; succinic acid; glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: Transcutol); diethylene glycol monoethyl ether; esters of saturated

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coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Capmul MCM; Capmul MCM and a non-ionic surfactant; and Capmul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant, e.g., Gelucire 44/14, can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1.

The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, Capmul MCM and Gelucire were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. See, e.g., Tables 13-17, below. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In illustrative embodiments of the invention, oils used to solubilize estradiol and to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, estradiol or progesterone (or both) is soluble in the oils at room temperature, although it may be desirable to warm the oils up until they are in a liquid state. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50 C, e.g., at or below 50 C, at or below 40 C, or at or below 50 C. In illustrative embodiments, Gelucire 44/14 is heated to about 65 C and Capmul MCM is heated to about 40 C to facilitate mixing of the oil and non-surfactant, although such heating is not necessary to dissolve the estradiol or progesterone. In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8 wt % or higher, or 1.0 wt % or higher.

Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, Capmul MCM, Capmul MCM C10, Capmul MCM C8, and Capmul MCM C8 EP. These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, Miglyol 810 and Miglyol 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, Capmul PG-8, Capmul PG-2L EP/NF, Capmul PG-8 NF, Capmul PG-12 EP/NF and Capryol. Other illustrative examples include Miglyol 840.

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others,

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Gelucire 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol. Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of Gelucire, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids. Specifically, a product information sheet for Myglyol by SASOL provides as the composition of fatty acids as follows:

Tests	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic acid (C14:0)	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

It will be understood that oils are often mixtures. So, for example, when an oil is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for Capmul MCM C8 describes Capmul MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher,

Mixtures of medium chain fatty acid glycerides, e.g., C6-C12, C8-C12, or C8-C10 fatty acid mono- and diglycerides or mono-, di-, and triglycerides are very well suited for dissolving estradiol; good results have been obtained with an oil that is predominantly a mixture of C8-C10 saturated fatty acid mono- and diglycerides. Longer chain glycerides appear to be not as well suited for dissolution of estradiol. On the other hand, high solubility of progesterone has been obtained in mixtures that are predominantly medium chain fatty acid triglycerides.

High solubility of estradiol has been obtained in 2-(2-Ethoxyethoxy)ethanol, e.g., Transcutol and in Propylene glycol monocaprylate, e.g., Capryol™ 90 (Gattefosse).

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone or estradiol. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., Capmul MCM) and polyethylene glycol glycerides (e.g., Gelucire) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65 C in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature or at lower temperatures as the mixture cools or even after it has cooled as temperatures above room temperature, e.g., about 20 C, are not required to solubilize the estradiol in preferred oils. The progesterone can also be added as the mixture cools, e.g., to below about 40 C or to below about 30 C, even down to room temperature.

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In various embodiments, estradiol is solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid esters or alcohols. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, Gelucire 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, e.g., Tables 13-17, below. Other non-ionic surfactants include, e.g., Labrasol® PEG-8 Caprylic/Capric Glycerides (Gattefosse) and Labarafil® corn/apricot oil PEG-6 esters (Gattefosse).

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

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As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises solubilized estradiol, progesterone at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of glycerol, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with Gelucire as surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following four formulations:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Formulation A- P: 50/EE: 0.25:		
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.17	0.26
Capmul MCM, NF	65.49	98.24
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00
Formulation B- P: 50/EE: 0.5:		
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.35	0.52
Capmul MCM, NF	65.32	97.98
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00
Formulation C - P: 100/EE: 0.5:		
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.17	0.52
Capmul MCM, NF	65.49	196.48
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00
Formulation D - P: 100/EE: 1:		
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.34	1.03
Capmul MCM, NF	65.32	195.97
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00
Formulation E- P: 200/EE: 2:		
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate	0.34	2.06
Capmul MCM, NF	65.32	391.94
Gelucire 44/14, NF	1.00	6.00
Total	100.00	600.00

*Note:

1.00 mg Estradiol equivalent to 1.03 mg Estradiol Hemihydrate.

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In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono- and diglycerides, such as Capmul MCM, and 0.5 to 10 wt % non-ionic surfactant, such as Gelucire 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opatint red and white, and, optionally, Miglyol 812.

Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g., 75%, 80%, 85%, 90%, or >95%, is solubilized appear to provide improved PK-related properties.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use;

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reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference -Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

In further solubility studies, estradiol was soluble at at least 6 mg/gm Miglyol Transcutol in ratios of 81:19 to 95:5, in Miglyol; ethanol at 91:11, and in Miglyol:Capmul PG8 at 88:11, but not in Miglyol:Transcutol at 96:4, Miglyol:Labra-sol at 70:30 to 80:20, or Miglyol:Capmul PG8 at 86:14.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60

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TABLE 2-continued

Ingredient	Solubility (mg/g)
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol: Miglyol: Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

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TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/ Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/ Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the

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solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

Example 7-1

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

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TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, Campul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/-2° C. Gelucire 44/14 may be added to the Campul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Campul MCM.

Heat may be removed from the Gelucire 44/14 and Campul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Campul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

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TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

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Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μ m, an X75 of 17.3 μ m, and an X25 of 5.3 μ m. The Beckman Device also yielded that the mean particle size is 11.8 μ m, the median particle size is 11.04 μ m, the mode particle size is 13.6 μ m, and the standard deviation is 7.8 μ m.

Example 12

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is heated to 65 C and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:			100.000	200.00 mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

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TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation. Alternatively, Gelucire 44/14 is heated to 65 C and Capmul MCM is heated to 40 C +/-5 C to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 40 C; the mixture is then passed through a colloid mill, e.g., three times.

Example 15

Study 352—Progesterone and Estradiol Combination Study under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	7.14	50.00
Estradiol Hemihydrate, USP Micronized	0.30	2.07
Capmul MCM, NF, USP	83.27	582.93
Gelucire 44/14, NF	9.29	650
Total	100.00	700

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

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Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ± 20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters C_{max}, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 24 subjects for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

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Corrected pharmacokinetic profile summaries are presented in Table 18, below, for progesterone.

TABLE 18

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	47.0	43.0	81.0 ± 82.8	117.7 ± 173.7
AUC _{0-t}	107.6	97.8	163.9 ± 136.5	191.1 ± 241.7
AUC _{0-∞}	110.7	110.0	173.5 ± 143.0	207.1 ± 250.3

*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters C_{max}, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 19, below for progesterone.

TABLE 19

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	2.3	3.0	2.9 ± 2.3	3.9 ± 3.4
AUC _{0-t}	8.4	10.9	11.2 ± 8.7	14.5 ± 11.0
AUC _{0-∞}	12.9	17.2	15.1 ± 9.0	19.6 ± 10.2

*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to Prometrium.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ± 5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

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Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C. +/−3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C. +/−10° C. The wedge temperature may be 38° C. +/−3° C. The drum cooling temperature may be 4° C. +/−2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about

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120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

Example 17

Solubility of Estradiol in Soy Bean Oil, Peanut Oil, and Safflower Oil

Data was obtained visually by making the mixtures described below, sonicating the mixtures, and then seeing if a clear solution resulted. If a clear solution was achieved, it was an indication of solubility at the level studied.

Procedures and Results:

Step 1.

0.3% of Estradiol suspension in each oil was prepared by adding 30 mg Estradiol to solvent and QS to 10 g. Samples were mixed on vortex for 2 hours, heated @ 50° C. for 30 minutes and then mixed for 1 hour more. All samples were still in suspension form.

Step 2.

Each sample was diluted to 0.24% (by adding 2.5 g more oil) and mixed for 2 hours and heated @50° C. for 30 min and mixed again for one hour. All the samples were still cloudy. Samples were kept at room temperature overnight to see if they precipitate or if un-dissolved API settles out. After 20 hours at room temperature, it was observed that all samples still had un-dissolved API.

Step 3.

Each sample was diluted to 0.2% (by adding 2.5 g more oil) and mixed 2 for hours and heated @50° C. for 30 min and mixed again for one hour. All the samples were still slightly cloudy, indicating that the estradiol was not completely dissolved.

TABLE 20

Ingredient	Estradiol Solubility (mg/g)	Estradiol Solubility (% w/w)
Peanut Oil	<2	<0.2
Safflower Oil	<2	<0.2
Soy Bean Oil	<2	<0.2

The solubility of estradiol in all three oils was less than 2 mg/g (0.2% w/w). This level of solubility is significantly below the solubility that the present inventors have discovered can be achieved in other oils, e.g., medium chain fatty acid esters, such as the mono/diglycerides, propylene glycol esters, and polyethylene glycol esters discussed above.

In sum, if no heat is used to dissolve estradiol in safflower oil, it will not go into solution. Given that the estradiol did not dissolve at 50 C, oils such as safflower oil will not be useful in the methods of the invention using medium chain fatty acid esters as described hereinabove.

Example 18

Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of Prometrium and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second

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study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37 C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from Prometrium. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from Prometrium is attached as FIG. 5.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

We claim:

1. A pharmaceutical composition comprising:

a solubilizing agent, the solubilizing agent comprising an effective amount of a C6-C12 oil;

1.0 mg estradiol or 1.03 mg estradiol hemihydrate, the estradiol or estradiol hemihydrate being at least about 90% solubilized in the solubilizing agent; and

100 mg progesterone;

wherein the estradiol or the estradiol hemihydrate, and the progesterone are uniformly dispersed in the solubilizing agent.

2. The pharmaceutical composition of claim 1, wherein the solubilizing agent is selected from at least one of monoglycerides, diglycerides, triglycerides, and combinations thereof, wherein the monoglycerides, diglycerides, and triglycerides are predominantly of C6-C12 fatty acid chain lengths.

3. The pharmaceutical composition of claim 2, wherein the monoglycerides, diglycerides, and triglycerides are >50% C6-C12 fatty acid chain lengths.

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4. A pharmaceutical composition comprising:

about 100 mg progesterone;

about 1.0 mg estradiol or 1.03 mg estradiol hemihydrate, the estradiol or estradiol hemihydrate being at least about 90% solubilized;

about 195.97 mg of monoglycerides and diglycerides of caprylic acid and capric acid (CAPMUL MCM); and about 3.0 mg of at least one of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, or lauroyl polyoxylglycerides (GELUCIRE 44/14);

wherein the estradiol or the estradiol hemihydrate, and the progesterone are uniformly dispersed in the solubilizing agent.

5. A method of treating a menopause-related symptom in a woman comprising administering an effective amount of pharmaceutical composition to a subject in need thereof, the pharmaceutical composition comprising:

about 100 mg progesterone;

about 1.0 mg estradiol or 1.03 mg estradiol hemihydrate, the estradiol or estradiol hemihydrate being at least about 90% solubilized;

about 195.97 mg of monoglycerides and diglycerides of caprylic acid and capric acid (CAPMUL MCM); and about 3.0 mg of at least one of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, or lauroyl polyoxylglycerides (GELUCIRE 44/14);

wherein the estradiol or the estradiol hemihydrate, and the progesterone are uniformly dispersed in the solubilizing agent.

6. The method of claim 5, wherein the pharmaceutical composition is administered as a continuous-combined therapy regimen.

7. The method of claim 5, wherein the pharmaceutical composition is administered a sequentially-combined therapy regimen.

8. A method of treating a vasomotor symptom in a woman comprising administering an effective amount of a pharmaceutical composition comprising:

1.0 mg estradiol or 1.03 mg estradiol hemihydrate, the estradiol or estradiol hemihydrate being at least about 90% solubilized in the solubilizing agent;

100 mg progesterone; and

a solubilizing agent, the solubilizing agent comprising an effective amount of a C6-C12 oil;

wherein the estradiol or the estradiol hemihydrate, and the progesterone are uniformly dispersed in the solubilizing agent; and

wherein the pharmaceutical composition is administered once daily for the treatment of symptoms associated with menopause.

9. The method of claim 8, wherein the pharmaceutical composition is administered as a continuous-combined therapy regimen.

10. The method of claim 8, wherein the pharmaceutical composition is administered as a sequentially-combined therapy regimen.

11. The method of claim 8, wherein the solubilizing agent is selected from at least one of monoglycerides, diglycerides, triglycerides, and combinations thereof, wherein the monoglycerides, diglycerides, and triglycerides are predominantly of C6-C12 fatty acid chain lengths.

12. The method of claim 11, wherein the monoglycerides, diglycerides, and triglycerides are >50% C6-C12 fatty acid chain lengths.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,006,222 B2
APPLICATION NO. : 14/099623
DATED : April 14, 2015
INVENTOR(S) : Brian A. Bernick et al.

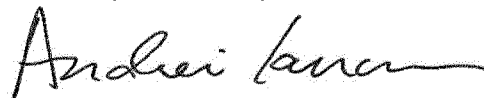
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-fifth Day of June, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu", written in a cursive style.

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT H



US009114145B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 9,114,145 B2**
(45) **Date of Patent:** ***Aug. 25, 2015**

(54) **NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
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(2013.01); **A61K 31/565** (2013.01)

(58) **Field of Classification Search**

USPC 514/169; 424/452
See application file for complete search history.

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Primary Examiner — Dennis J Parad

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Stockton; Marlan D. Walker

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are pro-
vided herein. Among others, the following formulations are
provided herein: solubilized estradiol without progesterone;
micronized progesterone without estradiol; micronized
progesterone with partially solubilized progesterone; solu-
bilized estradiol with micronized progesterone; solubilized
estradiol with micronized progesterone in combination with
partially solubilized progesterone; and solubilized estradiol
with solubilized progesterone.

18 Claims, 4 Drawing Sheets

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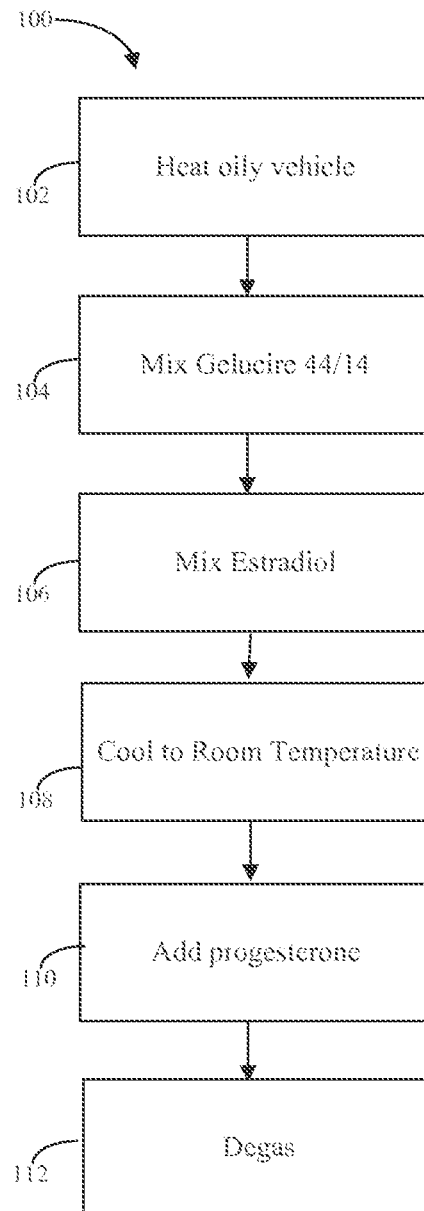


Fig. 1

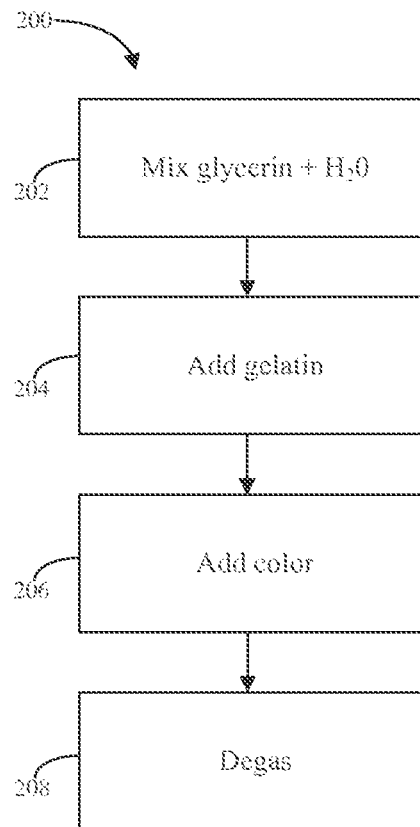


Fig. 2

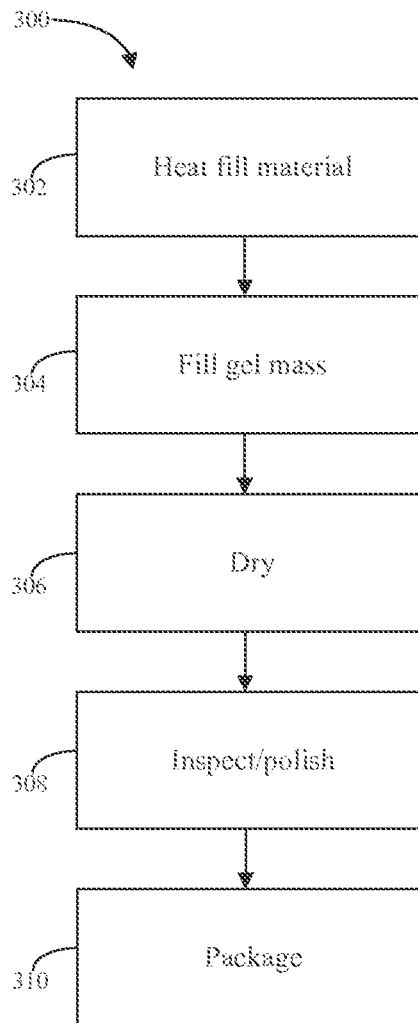


Fig. 3

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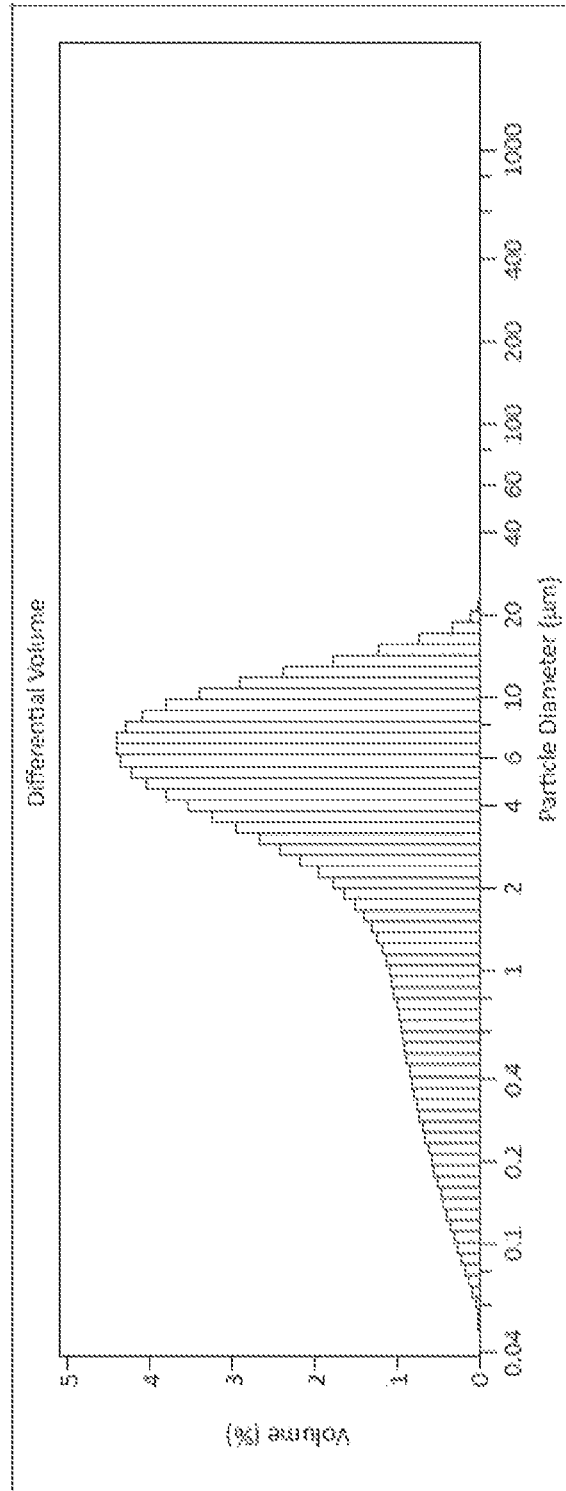


FIG. 4

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NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/099,545, entitled “NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES” which was filed on Dec. 6, 2013, which application is a divisional of U.S. patent application Ser. No. 13/684,002, entitled “NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES” which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which application claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled “NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES” which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled “ESTRADIOL FORMULATIONS” which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled “PROGESTERONE FORMULATIONS” which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as “Cyclic-Sequential” or “Sequentially-Combined HRT.” This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a

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constant dosage with both estrogen and progesterone taken daily, is called “continuous-combined HRT.” This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

5 Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

10 “Bio-identical” hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

15 These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

20 Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare’s urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY OF THE INVENTION

25 According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

30 The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

60 FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

65 FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

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DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

A. DEFINITIONS

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, T_{max} .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ C_{max} ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ T_{max} ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

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The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

B. DESCRIPTION AND PREFERRED EMBODIMENTS

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to

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about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from

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about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μ m to 2000 μ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

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Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol: Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Campul MCM; Capmul MCM and a non-ionic surfactant; and Campul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Campul MCM and Gelucire can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

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In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

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In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

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Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference - Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold

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cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol:Miglyol:Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

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As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

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For example, Campul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/-2° C. Gelucire 44/14 may be added to the Campul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Campul MCM.

Heat may be removed from the Gelucire 44/14 and Campul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Campul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is

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removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxy-1-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μm , an X75 of 7.442 μm , and an X25 of 1.590 μm . The Beckman Device also yielded that the mean particle size is 4.975 μm , the median particle size is 4.279 μm , the mode particle size is 6.453 μm , and the standard deviation is 3.956 μm . A graph of the particle distribution obtained is shown in FIG. 4.

Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μm , an X75 of 17.3 μm , and an X25 of 5.3 μm . The Beckman Device also yielded that the mean particle size is 11.8 μm , the median particle size is 11.04 μm , the mode particle size is 13.6 μm , and the standard deviation is 7.8 μm .

Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

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TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	INGRE-DIENT(S)	Label Claim (mg)	% w/w	Qty/Cap-sule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemi-hydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:			100.000	200.00 mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemi-hydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until

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dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 16

Progesterone and Estradiol Combination Study Under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla.) and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condi-

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tion, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ± 20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ± 5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

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With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degasing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+/-3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/-10° C. The wedge temperature may be 38° C.+/-3° C. The drum cooling temperature may be 4° C.+/-2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A method of treating a menopause-related symptom in a woman comprising: administering to the woman an effective amount of a pharmaceutical composition, the pharmaceutical composition comprising:

solubilized estradiol;
suspended progesterone; and
a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;

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wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises an effective amount at least one of mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid.

2. The method of claim 1, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

3. The method of claim 1, wherein the formulation is formulated as a gelatin capsule.

4. The method of claim 1, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

5. The method of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

6. The method of claim 1, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and a 2 mg estradiol tablet.

7. A method of treating a menopause symptom in a woman comprising: administering a pharmaceutical composition to the woman, the pharmaceutical composition comprising:

solubilized estradiol;

suspended progesterone; and

a solubilizing agent, the solubilizing agent comprising an effective amount mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid;

wherein the estradiol and the suspended progesterone are present in the solubilizing agent, the estradiol and progesterone are uniformly dispersed, and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the estradiol does not precipitate for at least 14 days.

8. The method of claim 7, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

9. The method of claim 7, wherein the formulation is formulated as a gelatin capsule.

10. The method of claim 7, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

11. The method of claim 7, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

12. The method of claim 7, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and a 2 mg estradiol tablet.

13. A method of treating a menopause symptom comprising: administering an effective amount of a pharmaceutical composition to a woman, the pharmaceutical composition comprising:

solubilized estradiol;

suspended progesterone; and

a solubilizing agent, the estradiol being stable in the solubilizing agent for at least 14 days;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent;

wherein the estradiol and progesterone are uniformly dispersed;

wherein at least about 90% of the estradiol is solubilized in the solubilizing agent, and

wherein the solubilizing agent comprises an effective amount mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid.

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14. The method of claim 13, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

15. The method of claim 13, wherein the formulation is formulated as a gelatin capsule.

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16. The method of claim 13, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

17. The method of claim 13, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

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18. The method of claim 13, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and a 2 mg estradiol tablet.

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* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,114,145 B2
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DATED : August 25, 2015
INVENTOR(S) : Brian A. Bernick et al.

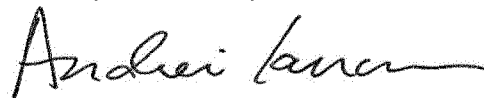
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT I



US009114146B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 9,114,146 B2**
(45) **Date of Patent:** ***Aug. 25, 2015**

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

15 Claims, 4 Drawing Sheets

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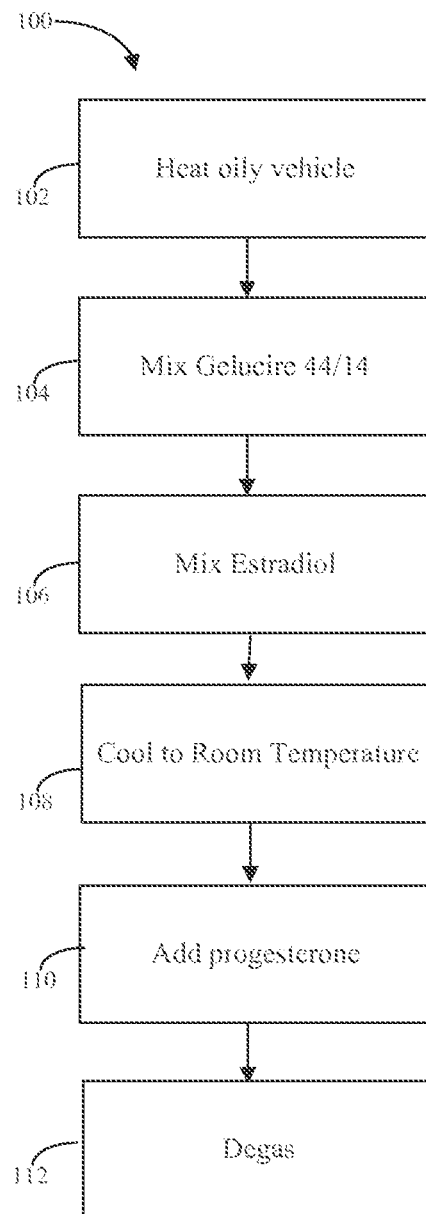


Fig. 1

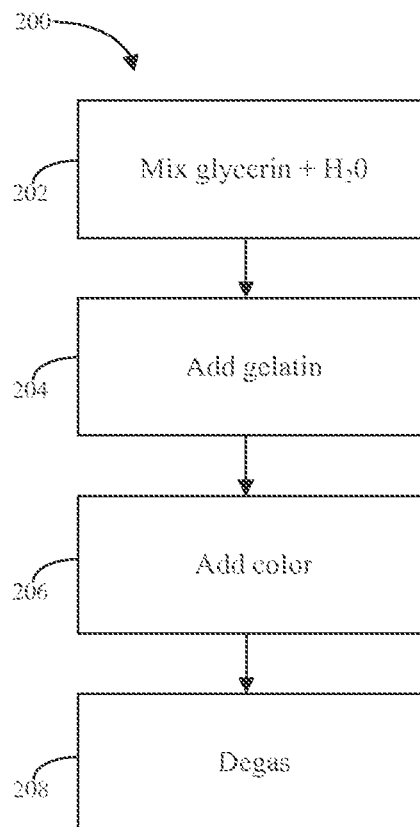


Fig. 2

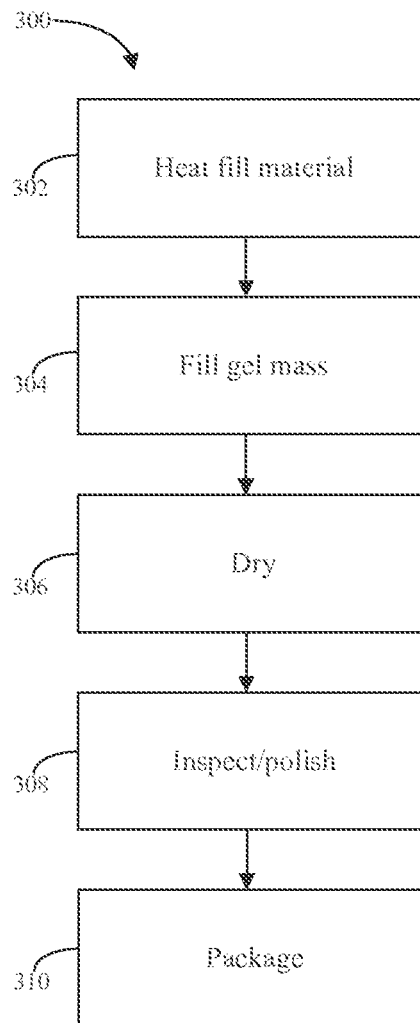


Fig. 3

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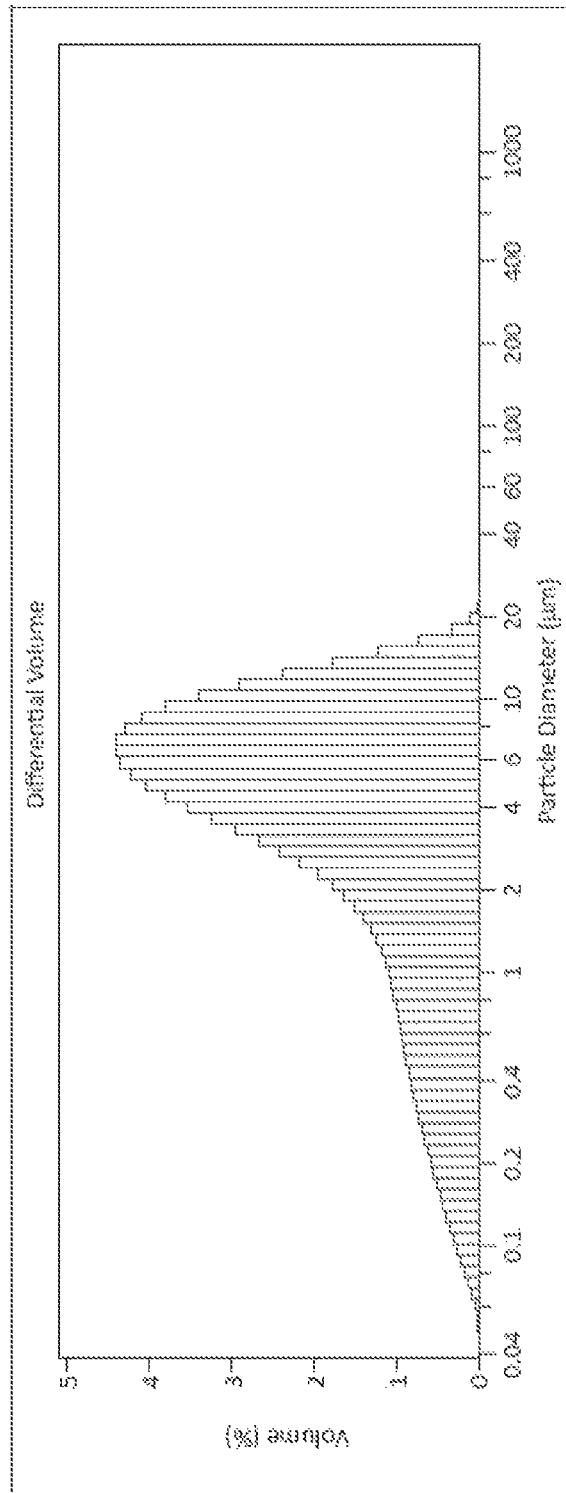


FIG. 4

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NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/099,545, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Dec. 6, 2013, which application is a divisional of U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which claims priority to the following U.S. Provisional patent applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a

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constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

5 Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

10 "Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

15 These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

20 Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY OF THE INVENTION

35 According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

40 The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

60 FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

65 FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

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DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

A. Definitions

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, T_{max} .

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, " C_{max} " as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, " T_{max} " as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating

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pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "oil" as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

"Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution.

"Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

B. Description and Preferred Embodiments

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra-

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and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125,

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1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μ m to 2000 μ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

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Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol; Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Campul MCM; Capmul MCM and a non-ionic surfactant; and Campul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Campul MCM and Gelucire can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other

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solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2, 3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may

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contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and

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filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference—Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

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TABLE 3

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:	6	Clear, after 14 days
Capmul PG8 (5:80:15)		
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol:Miglyol:Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

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As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

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For example, Campul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/-2° C. Gelucire 44/14 may be added to the Campul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Campul MCM.

Heat may be removed from the Gelucire 44/14 and Campul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Campul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is

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removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μm , an X75 of 7.442 μm , and an X25 of 1.590 μm . The Beckman Device also yielded that the mean particle size is 4.975 μm , the median particle size is 4.279 μm , the mode particle size is 6.453 μm , and the standard deviation is 3.956 μm . A graph of the particle distribution obtained is shown in FIG. 4.

Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μm , an X75 of 17.3 μm , and an X25 of 5.3 μm . The Beckman Device also yielded that the mean particle size is 11.8 μm , the median particle size is 11.04 μm , the mode particle size is 13.6 μm , and the standard deviation is 7.8 μm .

Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

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TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:			100.000	200.00mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until

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dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 16

Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla.) (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condi-

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tion, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ± 20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ± 5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

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With reference to FIG. 2, softgel capsule, i.e. gel mass, production **200** is shown. Step **202** comprises mixing glycerin with water. The water used in step **202** may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **202** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step **204** comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **204** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step **204** to de-aerate.

Step **206** comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step **206** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step **208** comprises degassing. The resulting mixture from step **208** may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process **300** is shown. Step **302** comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+/-3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step **304** comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step **208** of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/-10° C. The wedge temperature may be 38° C.+/-3° C. The drum cooling temperature may be 4° C.+/-2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step **304** thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step **306** comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step **308** may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step **310** may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A pharmaceutical composition comprising:
solubilized estradiol;
suspended progesterone;
and a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;
wherein at least about 90% of the estradiol is solubilized in the solubilizing agent;

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and wherein the solubilizing agent comprises predominately a saturated C6-C12 oil.

2. The pharmaceutical composition of claim 1, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

3. The pharmaceutical composition of claim 1, wherein the formulation is formulated as a gelatin capsule.

4. The pharmaceutical composition of claim 1, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

5. The pharmaceutical composition of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

6. A pharmaceutical composition comprising:

solubilized estradiol;

suspended progesterone; and

a solubilizing agent, the solubilizing agent comprising predominately a saturated C6-C12 oil;

wherein the estradiol and the suspended progesterone are present in the solubilizing agent, the estradiol and progesterone are uniformly dispersed, and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the estradiol does not precipitate for at least 14 days.

7. The pharmaceutical composition of claim 6, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

8. The pharmaceutical composition of claim 6, wherein the composition is formulated as a gelatin capsule.

9. The pharmaceutical composition of claim 6, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

10. The pharmaceutical composition of claim 6, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

11. A method of treating menopause symptoms in a woman with a uterus comprising:

administering an effective amount of a pharmaceutical composition, the pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent, the estradiol and the suspended progesterone are uniformly dispersed and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises predominately a saturated C6-C12 oil.

12. The method of claim 11, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

13. The method of claim 11, wherein the composition is formulated in a gelatin capsule.

14. The method of claim 11, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

15. The method of claim 11, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,114,146 B2
APPLICATION NO. : 14/476040
DATED : August 25, 2015
INVENTOR(S) : Brian A. Bernick et al.

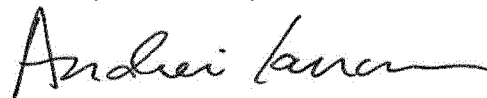
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu", written in a cursive style.

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT J



US009301920B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 9,301,920 B2**
(45) **Date of Patent:** ***Apr. 5, 2016**

(54) **NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
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This patent is subject to a terminal dis-
claimer.

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(51) **Int. Cl.**

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A61K 9/02 (2006.01)

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(58) **Field of Classification Search**

USPC 514/170, 899
See application file for complete search history.

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(57)

ABSTRACT

Estrogen and progesterone replacement therapies are pro-
vided herein. Among others, the following formulations are
provided herein: solubilized estradiol without progesterone;
micronized progesterone without estradiol; micronized
progesterone with partially solubilized progesterone; solubi-
lized estradiol with micronized progesterone; solubilized
estradiol with micronized progesterone in combination with
partially solubilized progesterone; and solubilized estradiol
with solubilized progesterone.

14 Claims, 5 Drawing Sheets

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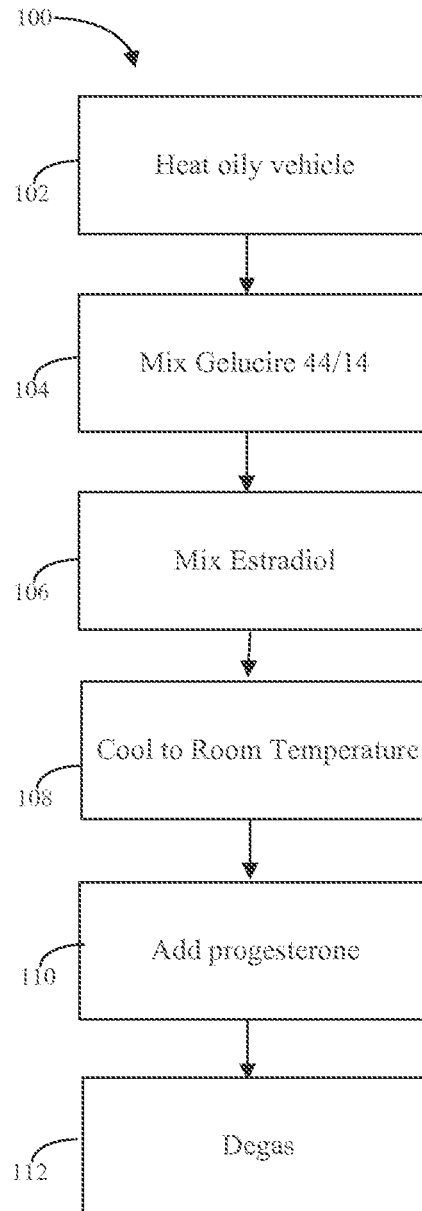


Fig. 1

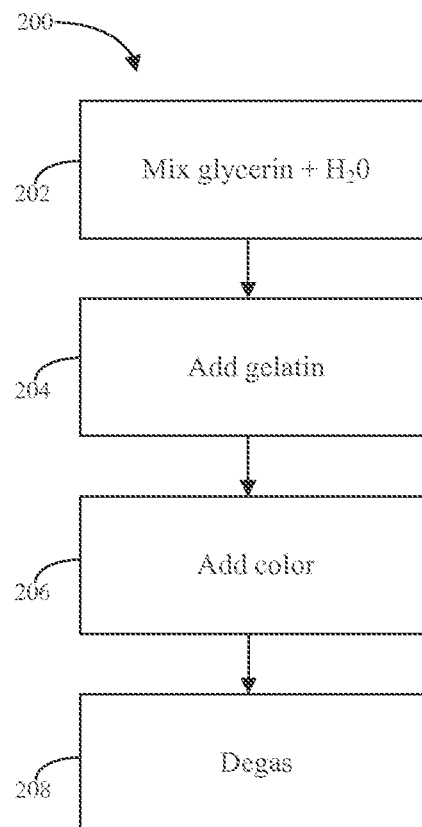


Fig. 2

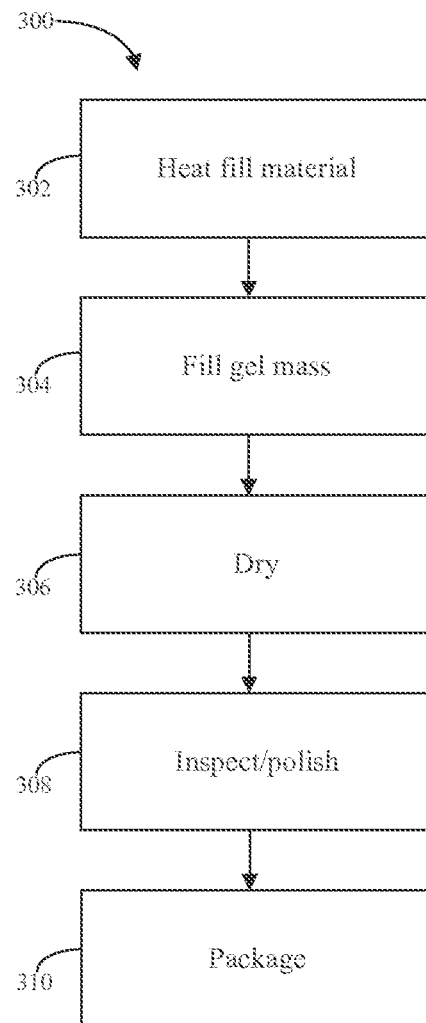


Fig. 3

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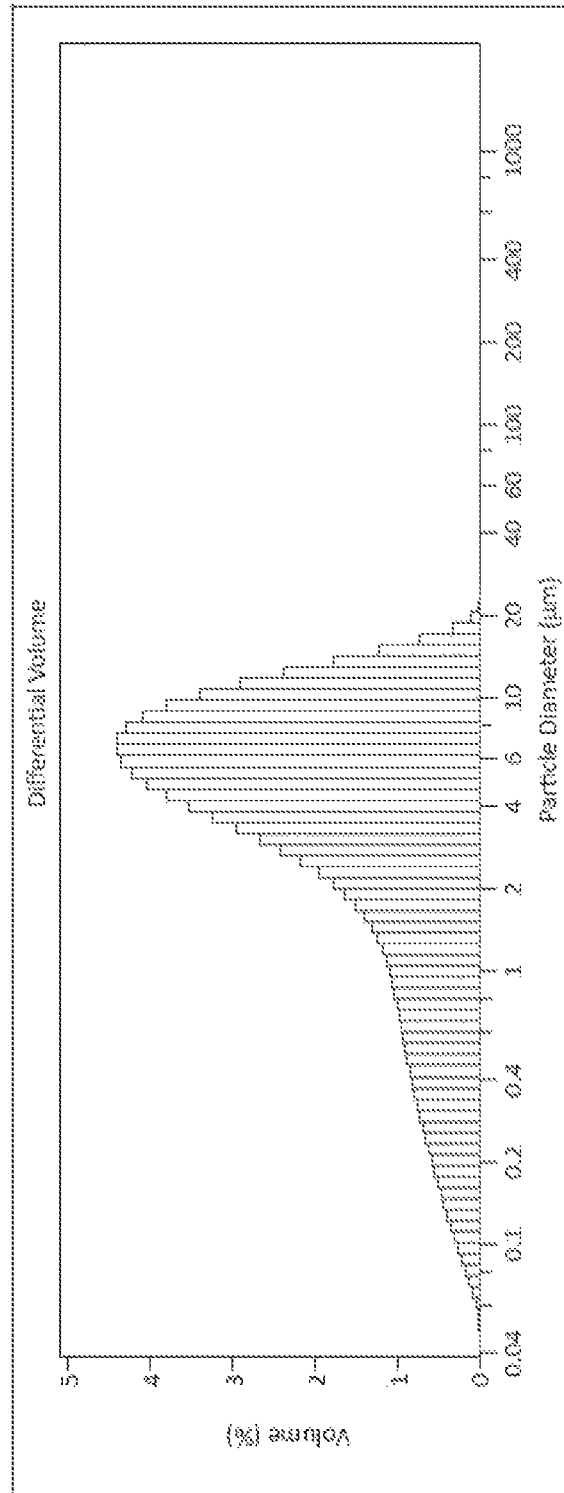


FIG. 4

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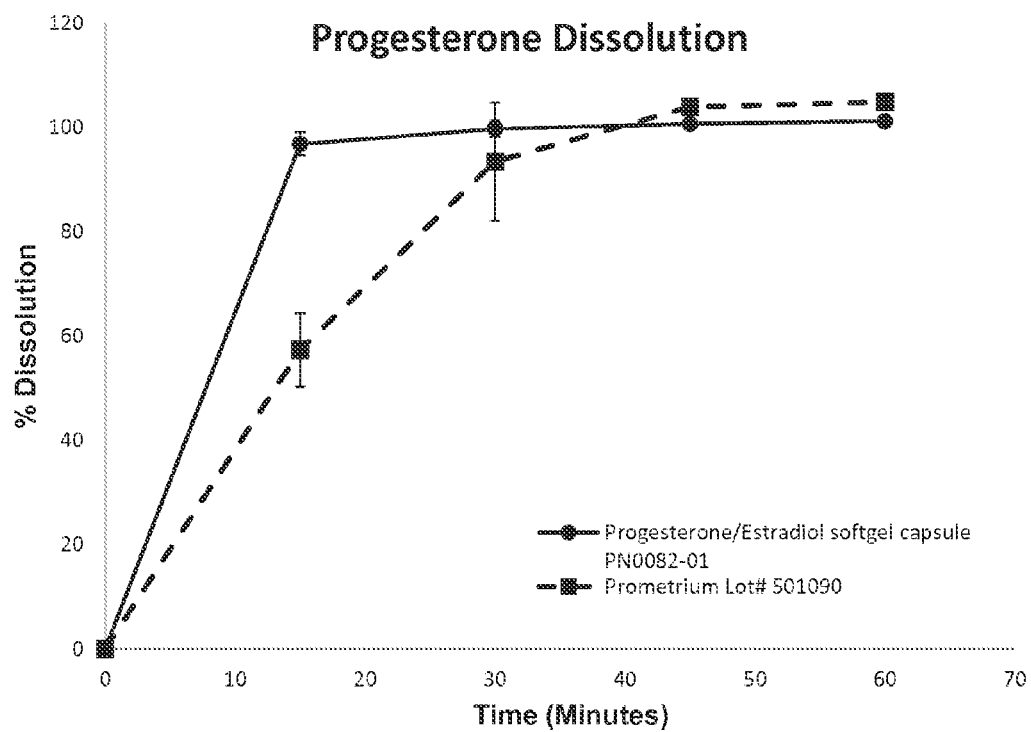
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FIG. 5

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NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to the following U.S. patent applications: U.S. application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES," which was filed on Nov. 21, 2012; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULA- TIONS," which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bod-

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ies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Prometrium was approved for sale in the United States on May 14, 1998 under NDA # NO19781. According to the prescribing information approved for this product (Rev June 2009) ("Prometrium prescribing information"), Prometrium comprises synthetic progesterone that is chemically identical to progesterone of human ovarian origin. Capsules comprise 100 mg or 200 mg of micronized progesterone. The inactive ingredients include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, and yellow and red dyes.

Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

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FIG. 5 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

Definitions

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, Cmax, and optionally, Tmax.

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “Cmax” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “Tmax” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, Cmax and, optionally, Tmax are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal especially a mammal, including human, subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without

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limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, such as an organic oil other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution, i.e., at least 98% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%, i.e., up to but not including 98% in solution.

As used herein, unless specified, estradiol includes estradiol in anhydrous and hemihydrate forms.

Description

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be

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desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %; estradiol is 0.1 to 0.8 wt %, e.g., 0.15 to 0.35 wt %.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

According to the Prometrium prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered Prometrium once a day for five days resulted in the mean PK parameters listed in the following table:

Parameter	Prometrium Capsules Daily Dose		
	100 mg	200 mg	300 mg
C_{max} (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
T_{max} (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
AUC_{0-10} (ng x hr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

In a particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations

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as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery

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and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of caproic fatty acid; caprylic fatty acid; capric fatty acid; tauric acid; myristic acid; linoleic acid; succinic acid; glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: Transcutol); diethylene glycol monoethyl ether; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

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In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Capmul MCM; Capmul MCM and a non-ionic surfactant; and Capmul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant, e.g., Gelucire 44/14, can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, Capmul MCM and Gelucire were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. See, e.g., Tables 13-17, below. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In illustrative embodiments of the invention, oils used to solubilize estradiol and to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, estradiol or progesterone (or both) is soluble in the oils at room temperature, although it may be desirable to warm the oils up until they are in a liquid state. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50 C., e.g., at or below 50 C., at or below 40 C., or at or below 50 C. In illustrative embodiments, Gelucire 44/14 is heated to about 65 C. and Capmul MCM is heated to about 40 C. to facilitate mixing of the oil and non-surfactant, although such heating is not necessary to dissolve the estradiol or progesterone. In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8 wt % or higher, or 1.0 wt % or higher.

Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, Capmul MCM, Capmul MCM C10, Capmul MCM C8, and Capmul MCM C8 EP. These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, Miglyol 810 and Miglyol 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, Capmul PG-8, Capmul PG-2L EP/NF, Capmul PG-8 NF, Capmul PG-12 EP/NF and Capryol. Other illustrative examples include Miglyol 840.

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others, Gelucire 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

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Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of Gelucire, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids. Specifically, a product information sheet for Myglyol by SASOL provides as the composition of fatty acids as follows:

	Tests				
	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic acid (C14:0)	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

It will be understood that oils are often mixtures. So, for example, when an oil is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for Capmul MCM C8 describes Capmul MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher,

Mixtures of medium chain fatty acid glycerides, e.g., C6-C12, C8-C12, or C8-C10 fatty acid mono- and diglycerides or mono-, di-, and triglycerides are very well suited for dissolving estradiol; good results have been obtained with an oil that is predominantly a mixture of C8-C10 saturated fatty acid mono- and diglycerides. Longer chain glycerides appear to be not as well suited for dissolution of estradiol. On the other hand, high solubility of progesterone has been obtained in mixtures that are predominantly medium chain fatty acid triglycerides.

High solubility of estradiol has been obtained in 2-(2-Ethoxyethoxy)ethanol, e.g., Transcutol and in Propylene glycol monocaprylate, e.g., Capryol™ 90 (Gattefosse).

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone or estradiol. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., Capmul MCM) and polyethylene glycol glycerides (e.g., Gelucire) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65 C. in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature or at lower temperatures as the mixture cools or even after it has cooled as temperatures above room temperature, e.g., about 20 C., are not required to solubilize the estradiol in preferred oils. The progesterone can also be added as the mixture cools, e.g., to below about 40 C. or to below about 30 C., even down to room temperature.

In various embodiments, estradiol is solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %).

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In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid esters or alcohols. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, Gelucire 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, e.g., Tables 13-17, below. Other non-ionic surfactants include, e.g., Labrasol® PEG-8 Caprylic/Capric Glycerides (Gattefosse) and Labarafil® corn/apricot oil PEG-6 esters (Gattefosse).

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formula-

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tions of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises solubilized estradiol, progesterone at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of glycerol, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with Gelucire as surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following four formulations:

Formulation A - P:50/EE:0.25:

Ingredient(s)	Amount (%) w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.17	0.26
Capmul MCM, NF	65.49	98.24
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00

Formulation B - P:50/EE:0.5:

Ingredient(s)	Amount (%) w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.35	0.52
Capmul MCM, NF	65.32	97.98
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00

Formulation C - P:100/EE:0.5:

Ingredient(s)	Amount (%) w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.17	0.52
Capmul MCM, NF	65.49	196.48
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00

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Formulation D - P:100/EE:1:

Ingredient(s)	Amount (%) w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.34	1.03
Capmul MCM, NF	65.32	195.97
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00

Formulation E - P:200/EE:2:

Ingredient(s)	Amount (%) w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate	0.34	2.06
Capmul MCM, NF	65.32	391.94
Gelucire 44/14, NF	1.00	6.00
Total	100.00	600.00

*Note:

1.00 mg Estradiol equivalent to 1.03 mg Estradiol Hemihydrate.

In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono- and diglycerides, such as Capmul MCM, and 0.5 to 10 wt % non-ionic surfactant, such as Gelucire 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opatint red and white, and, optionally, Miglyol 812.

Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g., 75%, 80%, 85%, 90%, or >95%, is solubilized appear to provide improved PK-related properties.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

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Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference - Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

In further solubility studies, estradiol was soluble at at least 6 mg/gm Miglyol Transcutol in ratios of 81:19 to 95:5, in

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Miglyol;ethanol at 91:11, and in Miglyol:Capmul PG8 at 88:11, but not in Miglyol:Transcutol at 96:4, Miglyol:Labrasol at 70:30 to 80:20, or Miglyol:Capmul PG8 at 86:14.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol: Miglyol: Capmul PG8 are stable and do not precipitate for at least 12 days.

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TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

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TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

Example 7-1

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, Capmul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/- 2° C. Gelucire 44/14 may be added to the Capmul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Capmul MCM.

Heat may be removed from the Gelucire 44/14 and Capmul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone

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may then be added to the Gelucire 44/14, Capmul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/ diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

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TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μ m, an X75 of 7.442 μ m, and an X25 of 1.590 μ m. The Beckman Device also yielded that the mean particle size is 4.975 μ m, the median particle size is 4.279 μ m, the mode particle size is 6.453 μ m, and the standard deviation is 3.956 μ m. A graph of the particle distribution obtained is shown in FIG. 4.

Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μ m, an X75 of 17.3 μ m, and an X25 of 5.3 μ m. The Beckman Device also yielded that the mean particle size is 11.8 μ m, the median particle size is 11.04 μ m, the mode particle size is 13.6 μ m, and the standard deviation is 7.8 μ m.

Example 12

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

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An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is heated to 65 C. and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:			100.000	200.00 mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation. Alternatively, Gelucire 44/14 is heated to 65 C. and Capmul MCM is heated to 40 C. +/-5 C. to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 40 C.; the mixture is then passed through a colloid mill, e.g., three times.

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Example 15

Study 352—Progesterone and Estradiol Combination Study Under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla.) (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

Ingredient(s)	Amount (%) w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	7.14	50.00
Estradiol Hemihydrate, USP	0.30	2.07
Micronized Capmul MCM, NF, USP	83.27	582.93
Gelucire 44/14, NF	9.29	650
Total	100.00	700

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout

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the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ± 20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters C_{max}, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 24 subjects for the test product and reference product. In general, bio-availability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 18, below, for progesterone.

TABLE 18

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)				
Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	47.0	43.0	81.0 ± 82.8	117.7 ± 173.7
AUC _{0-t}	107.6	97.8	163.9 ± 136.5	191.1 ± 241.7
AUC _{0-∞}	110.7	110.0	173.5 ± 143.0	207.1 ± 250.3

*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study Under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the

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high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters C_{max} , AUC_{0-t} & $AUC_{0-\infty}$ were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 19, below for progesterone.

TABLE 19

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)				
Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean \pm Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C_{max}	2.3	3.0	2.9 ± 2.3	3.9 ± 3.4
AUC_{0-t}	8.4	10.9	11.2 ± 8.7	14.5 ± 11.0
$AUC_{0-\infty}$	12.9	17.2	15.1 ± 9.0	19.6 ± 10.2

*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to Prometrium.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to $40^{\circ}\text{C} \pm 5^{\circ}\text{C}$. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 .

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means.

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Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Heating may be performed until the temperature reaches $80^{\circ}\text{C} \pm 5^{\circ}\text{C}$.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to $30^{\circ}\text{C} \pm 3^{\circ}\text{C}$. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of $55^{\circ}\text{C} \pm 10^{\circ}\text{C}$. The wedge temperature may be $38^{\circ}\text{C} \pm 3^{\circ}\text{C}$. The drum cooling temperature may be $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness $0.85\text{ mm} \pm 0.05\text{ mm}$ using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight $\pm 5\%$ (i.e., $650 \pm 33\text{ mg}$ and $325 \pm 16.3\text{ mg}$).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

Example 17

Solubility of Estradiol in Soy Bean Oil, Peanut Oil, and Safflower Oil

Data was obtained visually by making the mixtures described below, sonicating the mixtures, and then seeing if a clear solution resulted. If a clear solution was achieved, it was an indication of solubility at the level studied.

Procedures and Results:

Step 1.

0.3% of Estradiol suspension in each oil was prepared by adding 30 mg Estradiol to solvent and QS to 10 g. Samples were mixed on vortex for 2 hours, heated @ 50°C . for 30 minutes and then mixed for 1 hour more. All samples were still in suspension form.

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Step 2.

Each sample was diluted to 0.24% (by adding 2.5 g more oil) and mixed for 2 hours and heated @ 50° C. for 30 min and mixed again for one hour. All the samples were still cloudy. Samples were kept at room temperature overnight to see if they precipitate or if un-dissolved API settles out. After 20 hours at room temperature, it was observed that all samples still had un-dissolved API.

Step 3.

Each sample was diluted to 0.2% (by adding 2.5 g more oil) and mixed 2 for hours and heated @ 50° C. for 30 min and mixed again for one hour. All the samples were still slightly cloudy, indicating that the estradiol was not completely dissolved.

TABLE 20

Ingredient	Estradiol Solubility (mg/g)	Estradiol Solubility (% w/w)
Peanut Oil	<2	<0.2
Safflower Oil	<2	<0.2
Soy Bean Oil	<2	<0.2

The solubility of estradiol in all three oils was less than 2 mg/g (0.2% w/w). This level of solubility is significantly below the solubility that the present inventors have discovered can be achieved in other oils, e.g., medium chain fatty acid esters, such as the mono/diglycerides, propylene glycol esters, and polyethylene glycol esters discussed above.

In sum, if no heat is used to dissolve estradiol in safflower oil, it will not go into solution. Given that the estradiol did not dissolve at 50 C., oils such as safflower oil will not be useful in the methods of the invention using medium chain fatty acid esters as described hereinabove.

Example 18

Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of Prometrium and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37 C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from Prometrium. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from Prometrium is attached as FIG. 5.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present dis-

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closure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

We claim:

1. A pharmaceutical formulation for administering estradiol and progesterone to a mammal in need thereof, comprising

solubilized estradiol,
solubilized progesterone,
suspended progesterone, and
an oil,

wherein each of the solubilized estradiol, the solubilized progesterone, and the suspended progesterone is present in the oil, and

wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids.

2. The pharmaceutical formulation of claim 1 wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, and wherein the medium chain fatty acid esters are predominantly esters of

C6 to C10 fatty acids.

3. The pharmaceutical formulation of claim 1 wherein the oil is predominantly mono- and diglycerides.

4. The pharmaceutical formulation of claim 1 wherein at least 90% of the total estradiol is solubilized.

5. The pharmaceutical formulation of claim 1 further comprising a surfactant.

6. The pharmaceutical formulation of claim 5 wherein the surfactant is a non-ionic surfactant.

7. The pharmaceutical formulation of claim 6 wherein the surfactant is lauroyl polyoxyl-32-glycerides.

8. The pharmaceutical formulation of claim 1 comprising: 30 to 35 wt % progesterone,
0.1 to 0.4 wt % estradiol

55 to 75 wt % of the oil, wherein the oil is predominantly medium chain fatty acid mono- and diglycerides, and 0.5 to 10wt % non-ionic surfactant.

9. The pharmaceutical formulation of claim 8 further comprising gelatin, glycerol, and coloring agents.

10. The pharmaceutical formulation of claim 1 wherein the progesterone is released more rapidly than progesterone in peanut oil.

11. The pharmaceutical formulation of claim 1 wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, and wherein the medium chain fatty acid esters are predominantly esters of C8 to C12 fatty acids.

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12. The pharmaceutical formulation of claim 1 wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, and wherein the medium chain fatty acid esters are predominantly esters of C8 to C10 fatty acids.

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13. A method of treating at least one progesterone-deficient state in a mammal in need of treatment comprising administering an effective amount of a pharmaceutical formulation of claim 1.

14. A method of treating at least one estrogen-deficient state in a mammal in need of treatment comprising administering an effective amount of a pharmaceutical formulation of claim 1.

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* * * * *

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,301,920 B2
APPLICATION NO. : 13/843428
DATED : April 5, 2016
INVENTOR(S) : Brian A. Bernick et al.

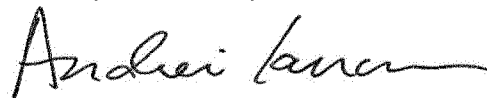
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT K



US010052386B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 10,052,386 B2**

(45) **Date of Patent:** ***Aug. 21, 2018**

(54) **PROGESTERONE FORMULATIONS**

(71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US); **Julia M. Amadio**, Boca Raton, FL (US); **Peter H. R. Persicaner**, Boca Raton, FL (US); **Janice Louise Cacace**, Miami, FL (US); **Thorsteinn Thorsteinsson**, West Palm Beach, FL (US); **Frederick D. Sancilio**, Palm Beach Gardens, FL (US)

(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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§ 371 (c)(1),

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Related U.S. Application Data

(63) Continuation of application No. 13/684,002, filed on Nov. 21, 2012, now Pat. No. 8,633,178, and a continuation-in-part of application No. 13/843,428, filed on Mar. 15, 2013, now Pat. No. 9,301,920, and a continuation of application No. PCT/US2013/023309, filed on Jan. 25, 2013, and a continuation of application No. 13/843,362, filed on Mar. 15, 2013.

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(51) **Int. Cl.**

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A61K 31/56 (2006.01)

A61K 47/44 (2017.01)

A61K 47/10 (2017.01)

A61K 47/14 (2017.01)

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A61K 9/48 (2006.01)

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(52) **U.S. Cl.**

CPC **A61K 47/14** (2013.01); **A61K 9/0014** (2013.01); **A61K 9/1075** (2013.01); **A61K 9/48** (2013.01); **A61K 9/4825** (2013.01); **A61K 31/565** (2013.01); **A61K 31/566** (2013.01); **A61K 31/57** (2013.01); **A61K 31/573** (2013.01); **A61K 45/06** (2013.01); **A61K 47/10** (2013.01)

(58) **Field of Classification Search**

CPC **A61K 31/57**; **A61K 47/44**; **A61K 47/10**
See application file for complete search history.

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Primary Examiner — Samira Jean-Louis

(74) Attorney, Agent, or Firm — Sterne Kessler Goldstein & Fox; Matthew Bodenstein

(57) **ABSTRACT**

Various pharmaceutical formulations are disclosed herein. For example, a pharmaceutical formulation is disclosed comprising ultra-micronized progesterone.

40 Claims, 6 Drawing Sheets

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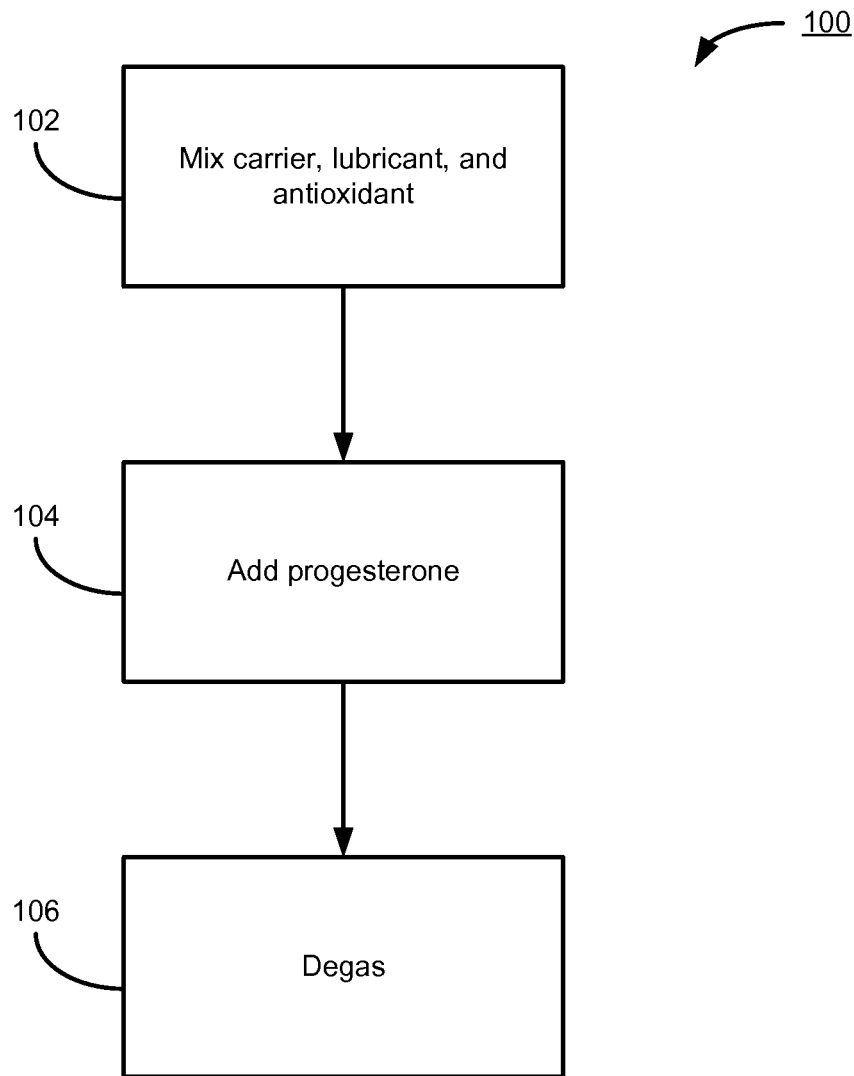


FIG. 1

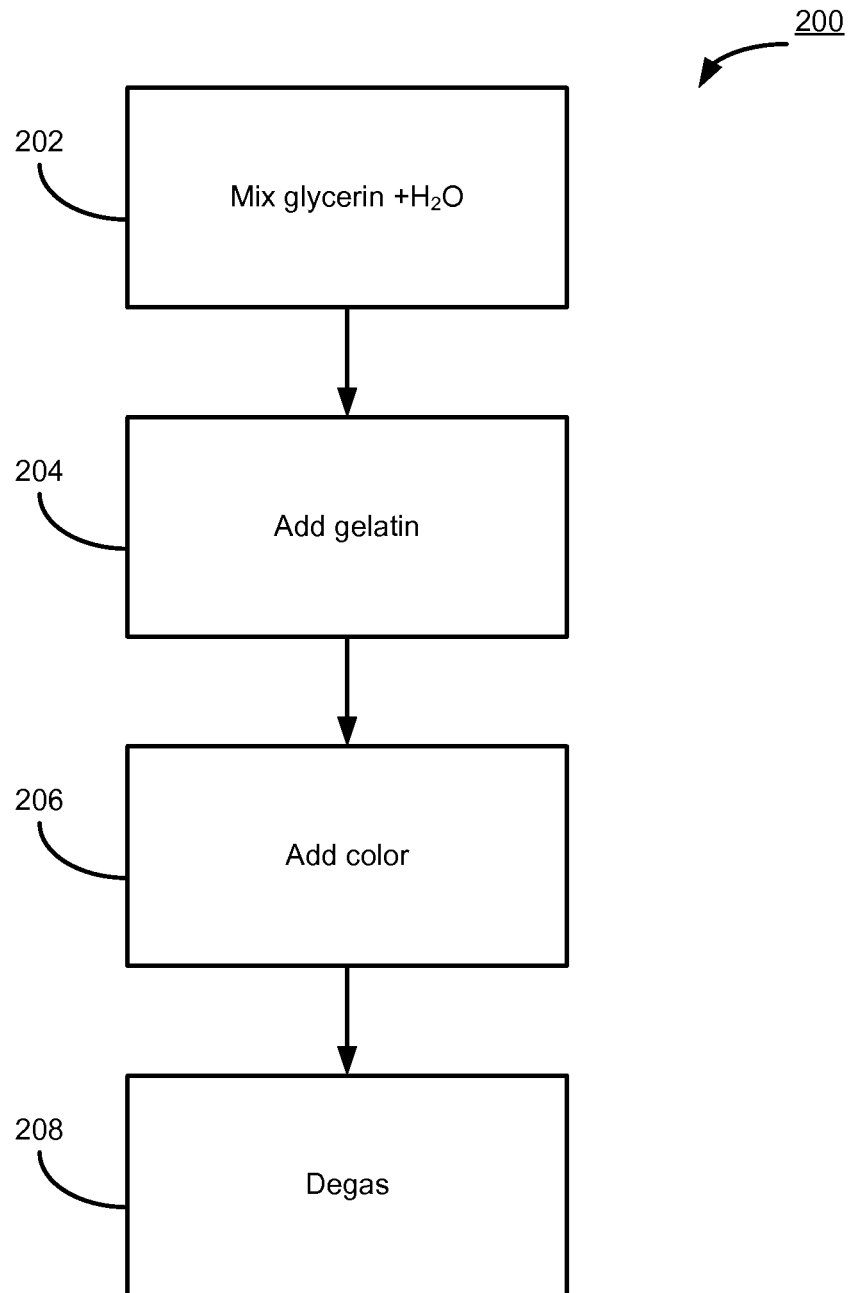


FIG. 2

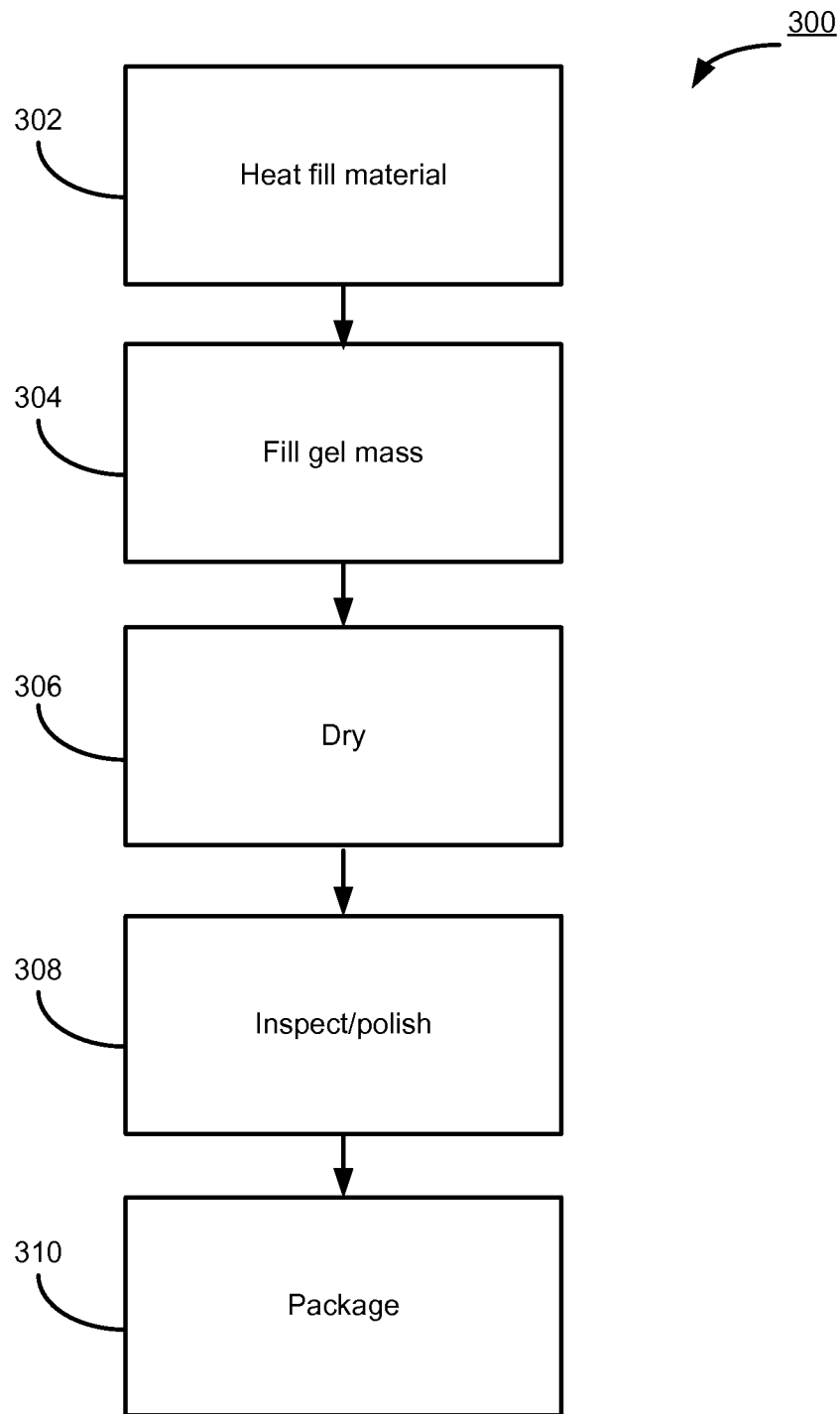
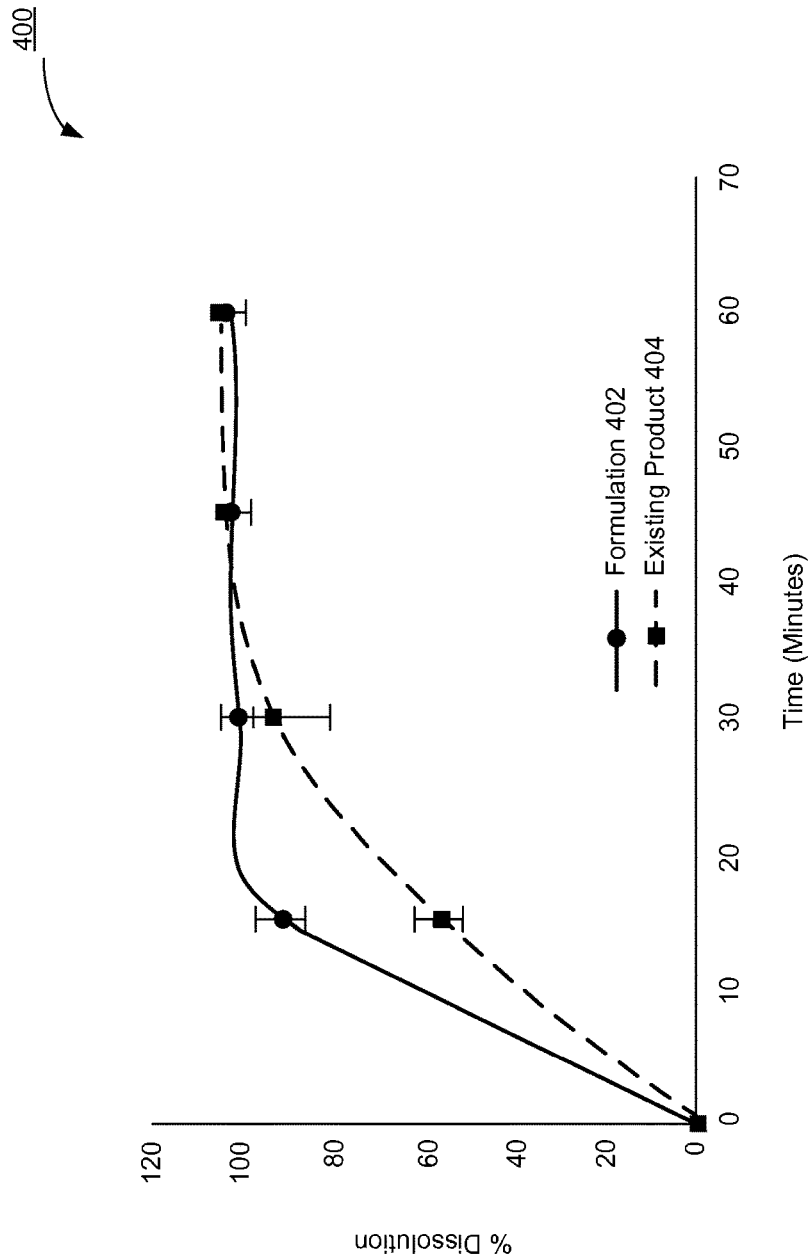


FIG. 3



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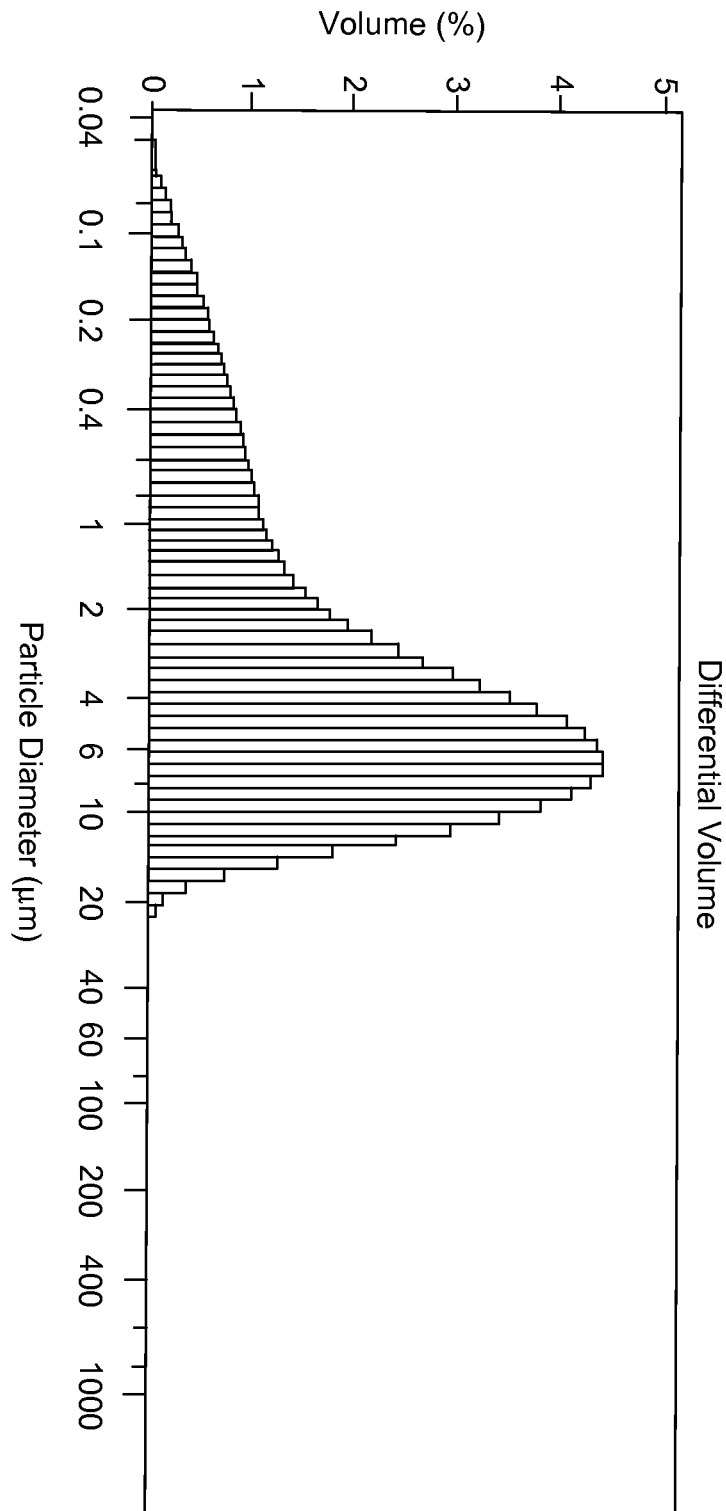


FIG. 5

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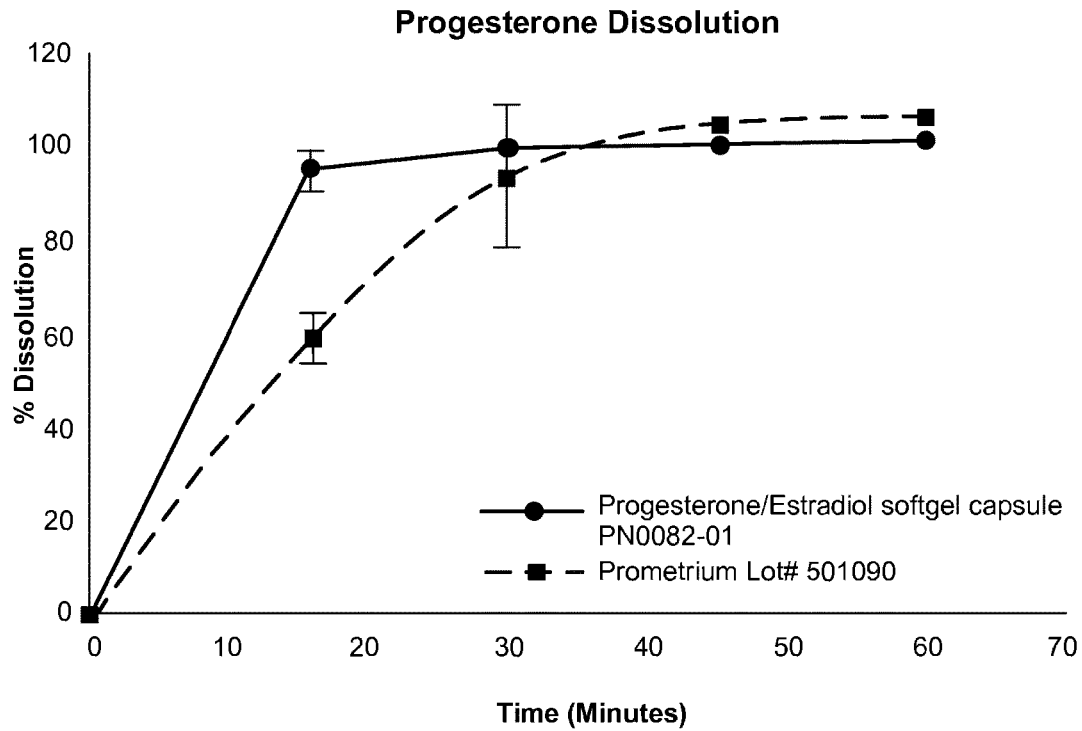


FIG. 6

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PROGESTERONE FORMULATIONS**CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a National Stage application under 35 U.S.C. § 371 of International Application Ser. No. PCT/US2013/046442, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 18, 2013, and claims priority to the following U.S. Patent Applications: U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS," which was filed on Jun. 20, 2012; U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Nov. 21, 2012; U.S. Patent Application Ser. No. PCT/US2013/023309, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Jan. 25, 2013; U.S. patent application Ser. No. 13/843,362, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Mar. 15, 2013; and U.S. patent application Ser. No. 13/843,428, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Mar. 15, 2013. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF INVENTION

The disclosure relates to progesterone formulations. Various progesterone formulations may be used in hormone therapies for menopausal, peri-menopausal and post-menopausal females, for example, to mitigate side effects from estrogen replacement therapy. In addition, various progesterone formulations may be used to prevent preterm delivery in pregnant women having a shortened cervix.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to supplement hormone levels in women who lack adequate hormone production. It can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones.

HRT is available in various forms. One therapy involves administration of low dosages of one or more estrogen(s) or one or more chemical analogues. Another involves administration of progesterone or one or more chemical analogues. Among other effects, progesterone administration acts to mitigate certain undesirable side effects from estradiol administration or naturally-occurring elevated blood levels including endometrial hyperplasia (thickening) and prevention or inhibition of endometrial cancer. Progesterone is a C-21 steroidal sex hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen. Like other steroids, progesterone consists of four interconnected cyclic hydrocarbons. Progesterone is hydrophobic, having a reported aqueous solubility of 0.007±0.0 mg/ml. Progesterone is poorly absorbed when administered orally.

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Conventional progesterone therapeutics include the administration of PROMETRIUM (progesterone, USP) (Abbott Laboratories, Chicago, Ill.). PROMETRIUM is an FDA-approved drug, formulated in a peanut oil-based medium, containing micronized progesterone, but with a relatively large particle size fraction.

The active ingredient is considered to be structurally identical to naturally occurring progesterone produced by a woman's body (also known as a "bioidentical").

Clinical trials involving PROMETRIUM have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean pharmacokinetic parameters listed in Table 1 (see Table 1, package insert for PROMETRIUM).

TABLE 1

Pharmacokinetic Parameters of PROMETRIUM Capsules			
Parameter	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
C_{max} (ng/ml)	17.3 ± 21.9	38.1 ± 37.8	60.6 ± 72.5
T_{max} (hr)	1.5 ± 0.8	2.3 ± 1.4	1.7 ± 0.6
AUC (0-10)(ngxh/ml)	43.3 ± 30.8	101.2 ± 66.0	175.7 ± 170.3

The unusually high variability in the C_{max} and AUC, as evidenced by the large reported standard deviation, indicates that a significant percentage of patients are overdosed or receive a sub-optimal dose.

The presence of peanut oil in the formulation excludes patients who are allergic to peanut oil. Peanut oil, like other peanut products, may act as an allergen. Indeed, there is a portion of the population that has severe reactions to peanut oil. Peanut allergies are becoming a significant health concern. Food allergies are a leading cause of anaphylaxis, with approximately 200 deaths occurring annually in the United States. While incidence and prevalence are not entirely known, it is suspected that about 6% of children and 4% of adults in North America are affected by food allergies. Many food allergies experienced by children are generally outgrown in adulthood with the exception of peanut allergies.

Progesterone and its analogues can be used to treat a variety of medical conditions, including acute diseases or disorders, as well as chronic diseases and disorders associated with long-term declines of natural progesterone levels.

Accordingly, improved formulations of progesterone would be advantageous.

SUMMARY OF THE INVENTION

Various pharmaceutical formulations are disclosed herein. For example, pharmaceutical formulations are disclosed comprising ultra-micronized progesterone. Moreover, pharmaceutical formulations are disclosed comprising formulations of ultra-micronized progesterone, wherein the ultra-micronized progesterone is combined with a suitable excipient.

Thus, in various illustrative embodiments, the invention comprises an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical ingredient, in micronized form, in solubilized form, or in micronized and partially soluble form in a carrier that comprises a medium chain fatty

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acid-glycol ester or mixtures thereof and a non-ionic surfactant comprising a polyethylene glycol fatty acid ester. In some such embodiments the progesterone is ultra-micronized. In some such embodiments, at least about 80 wt % of the total progesterone is micronized. The fatty acids can be predominantly (>50 wt %): C6 to C12 fatty acids, C6 to C10 fatty acids, C8 to C12 fatty acids, or C8 to C10 fatty acids, the esters can be mono-, di-, or triesters or mixtures thereof, and the glycols can be glycerol, polyethylene glycol or propylene glycol or mixtures thereof. Some embodiments comprise a non-ionic surfactant that comprises C8 to C18 fatty acid esters of glycerol and polyethylene glycol.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings are included to provide a further understanding of the disclosure and are incorporated in and constitute a part of this specification, illustrate embodiments of the disclosure, and together with the description serve to explain the principles of the disclosure.

FIG. 1 illustrates a process to produce fill material in accordance with various embodiments;

FIG. 2 illustrates a process to produce softgel capsules in accordance with various embodiments;

FIG. 3 illustrates a process to produce softgel capsules in accordance with various embodiments; and

FIG. 4 illustrates a dissolution study of a formulation in accordance with various embodiments.

FIG. 5 illustrates a graph of the particle distribution obtained in Example 10.

FIG. 6 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

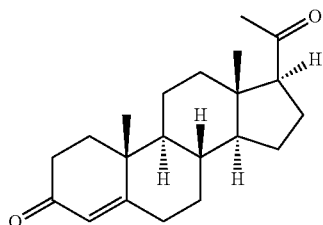
According to various embodiments, a pharmaceutical formulation comprising ultra-micronized progesterone is provided. As described in detail here, various carriers, lubricants, and other excipients may be included. In further embodiments, ultra-micronized progesterone formulations provide improved bioavailability and other pharmacokinetic improvements.

Definitions

Unless otherwise specified, the following definitions apply.

The term “ultra-micronized progesterone,” as used herein, includes micronized progesterone having an X50 value below about 20 microns and/or having an X90 value below about 25 microns.

A chemical structure of progesterone is depicted below:



The term “administer,” “administration,” “deliver” or “delivery” (collectively “administration”), as used herein,

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means administration to the body via, without limitation, tablets, capsules, softgel capsules, injections, transdermal patches, creams, gels, vaginal suppositories including gels or other mechanisms known in the art or hereinafter developed. The term “administration” may also mean direct application of softgel contents into the vagina, such as by accessing the softgel contents opening or rupturing the softgel capsule to liberate the contents therein.

The term “X50,” as used herein, means that half of the particles in a sample are smaller in diameter than a given number. For example, ultra-micronized progesterone having an X50 of 5 microns means that, for a given sample of ultra-micronized progesterone, half of the particles have a diameter of less than 5 microns. In that regard, similar terms, in the form XXX mean that YY percent of the particles in the sample are smaller in diameter than a given number. For example, X90 means that ninety percent of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances. For further illustration, C6-C14 fatty acids, C6-C12 fatty acids, and C8-C10 fatty acids are all medium chain fatty acids and may be used in instances in which this specification calls for use of medium chain fatty acids, e.g., medium chain fatty acid esters of glycerol or other glycols.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in gastric juices compared to PROMETRIUM.

The term “gastric juices” means the watery, acidic digestive fluid that is secreted by various glands in the mucous membrane of the stomach and consists chiefly of hydrochloric acid, pepsin, rennin, and mucin.

The term, “API,” as used herein, refers to active pharmaceutical ingredient. In formulations, the API is progesterone.

The term “excipients,” as used herein, refers to non-API substances such as carriers, solvents, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to humans according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “carrier,” as used herein, means any substance or mixture of substances that may be mixed with or contain an API (e.g., ultra-micronized progesterone).

The term “capsule,” as used herein, refers to a generally safe, readily dissolvable enclosure for carrying certain pharmaceutical products, and includes hard or soft shell capsules.

The term “softgel,” includes soft shell capsules, including soft-gelatin capsules and soft vegetable-based capsules, and soft capsules made from other materials providing the composition of such soft capsules are compatible with the formulations of the various embodiments described herein. A softgel may comprise two primary phases: a gel or vegetable-based capsule and a fill material of the pharmaceutical formulation as described herein.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (PK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} and optionally T_{max} .

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The terms “pharmacokinetics” and “pharmacokinetic measurements” include assessments and determinations to study absorption, distribution, metabolism, and excretion of a drug.

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone over time.

The term, “ C_{max} ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone over time.

The term, “ T_{max} ” as used herein, refers to the time that it takes for progesterone blood concentration to reach the maximum value.

Optionally, the term, “ $T_{1/2}$ ” as used herein, refers to the time that it takes for progesterone blood concentration to decline to one-half of the maximum level.

Collectively AUC, C_{max} , and optionally T_{max} and $T_{1/2}$, are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

DESCRIPTION

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone, and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %, based on the weight of the entire fill, i.e., the liquid pharmaceutical formulation.

Other embodiments disclosed herein further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, when compared to equal dosages of PROMETRIUM. Blood level variability is also compared at equal sampling times following administration.

According to the PROMETRIUM prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean PK parameters listed in the following table:

Parameter	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
C_{max} (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
T_{max} (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
AUC ₀₋₁₀ (ngxhr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

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In particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure include the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, “Progesterone-deficient States”) in a subject in need of treatment, and with a non-toxic effective amount of said formulations.

As used herein, the term “treatment”, or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, “prophylaxis” refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the “Beckman Device”) may be used to determine particle size. Particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module (“ULM”). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 nm. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant (“Coulter 1B”), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The

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Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

In various embodiments, ultra-micronized progesterone has an X50 value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns; and an X90 value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

In various embodiments, ultra-micronized progesterone is formulated with peanut and peanut-oil free excipients.

In various embodiments, the carrier is selected to enhance dissolution and suspension properties of progesterone. In further various embodiments, the carrier is selected to enhance absorption of the API by cells of a mammal. For example, certain carriers may be selected to enhance absorption of the other formulation components, including the API. Absorption may comprise absorption into any cell and particularly absorption into digestive system cells, such as intestinal cells, and cells of the female reproductive system, such as the vagina and the cervix. Selected mono/di/triglycerides are particularly suited to aid in cellular absorption.

In various embodiments, the carrier may comprise medium chain fatty acids. Suitable carriers include caproic fatty acid; caprylic fatty acid; capric fatty acid; lauric acid; myristic acid; linoleic acid; succinic acid; glycerin; propylene glycol; caprylic/capric triglycerides; caproic/caprylic/capric/lauric triglycerides; caprylic/capric/linoleic triglycerides; caprylic/capric/succinic triglycerides; polyethylene glycol; propylene glycol dicaprylate/dicaprate; and combinations and derivatives thereof.

Suitable carriers further include esters of saturated coconut and palm kernel oil and derivatives thereof, including fractionated coconut oils and palm kernel oils thereof; and triglycerides of fractionated vegetable fatty acids, and derivatives thereof and combinations thereof. In further various embodiments, the carrier may comprise one or more monoglycerides, diglycerides, triglycerides, and combinations thereof such a suitable carrier is available commercially under the trademark MIGLYOL (caprylic/capric triglyceride) (Sasol Germany, GmbH). MIGLYOL products comprise esters of saturated coconut and palm kernel oil-derived caprylic and capric fatty acids, glycerin and/or propylene glycol. Suitable MIGLYOL products include MIGLYOL 810 (Caprylic/Capric Triglyceride) MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 818 (Caprylic/Capric/Linoleic Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride).

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Additional examples include a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the CAPMUL brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol:Transcutol); diethylene glycol monoethyl ether; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof. In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL; TRANSCUTOL, MIGLYOL and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM and a non-ionic surfactant; and CAPMUL MCM and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for suspension and/or solubilization of progesterone. CAPMUL MCM and a non-ionic surfactant, e.g., GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, CAPMUL MCM and GELUCIRE were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. Thus, useful ratios can be, e.g., 8:1 or greater, e.g., 60 to 70:1.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In illustrative embodiments, oils used to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, progesterone is soluble in the oils at room temperature, although it may be desirable to warm certain oils initially during manufacture to improve viscosity. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50° C., e.g., at or below 50° C., at or below 40° C., or at or below 50° C. In illustrative embodiments, GELUCIRE 44/14 is heated to about 65° C. and CAPMUL MCM is heated to about 40° C. to facilitate mixing of the oil and non-ionic surfactant, although such heating is not necessary to dissolve the estradiol or progesterone.

In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8

wt % or higher, or 1.0 wt % or higher. Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, CAPMUL MCM, CAPMUL MCM C10 (Glyceryl Monocaprate), CAPMUL MCM C8 (Glyceryl Monocaprylate), and CAPMUL MCM C8 EP (Glyceryl Monocaprylate). These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, MIGLYOL 810 and MIGLYOL 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, CAPMUL PG-8, CAPMUL PG-2L EP/NF (Propylene Glycol Dilaurate), CAPMUL PG-8 NF (Propylene Glycol Monocaprylate), CAPMUL PG-12 EP/NF (Propylene Glycol Monolaurate) and CAPRYOL (Propylene glycol monocaprylate (type II) NF). Other illustrative examples include MIGLYOL 840 (Propylene Glycol Dicaprylate/Dicaprate).

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others, GELUCIRE 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol. Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of GELUCIRE, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids.

It will be understood that commercially available fatty acid esters of glycerol and other glycols are often prepared from natural oils and therefore may comprise components additional to the fatty acid esters that comprise the predominant (by weight) component(s) and that therefore are used to characterize the product. Such other components may be, e.g., other fatty acid triglycerides, mono- and diesters, free glycerol, or free fatty acids. So, for example, when an oil/solubilizing agent is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for CAPMUL MCM C8 describes CAPMUL MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher.

By way of further example, MIGLYOL 812 is generally described as a C8-C10 triglyceride because the fatty acid composition is at least about 80% caprylic (C8) acid and capric (C10) acid. However, it can also comprise small amounts of other fatty acids, e.g., less than about 5% of caproic (C6) acid, lauric (C12) acid, and myristic (C14) acid.

Specifically, a product information sheet for MIGLYOL by SASOL provides the composition of fatty acids as follows:

Tests	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic (C14:0) acid	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

Where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in C8-C10 triglycerides, and a thickening agent, it will be understood that the fatty acid esters component of the formulation may be, e.g., MIGLYOL 812 or a similar product.

By way of further illustration, GELUCIRE 44/14 is generally described as lauroyl polyoxyl-32 glycerides, i.e., polyoxyethylene 32 lauric glycerides (which is a mixture of mono-, di-, and triesters of glycerol and mono- and diesters of PEGs) because the fatty acid composition is 30 to 50% lauric acid and smaller amounts of other fatty acids, e.g., up to 15% caprylic acid, up to 12% capric acid, up to 25% myristic acid, up to 25% palmitic acid, and up to 35% stearic acid. The product may also contain small amounts of non-esterified glycols. Where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising C8 to C18 fatty acid esters of glycerol and polyethylene glycol, it will be understood that the thickening agent component of the formulation may be, e.g., GELUCIRE 44/14 or a similar product.

Similarly, where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising PEG-6 stearate, ethylene glycol palmitostearate, and PEG-32 stearate, it will be understood that the thickening agent component of the formulation may be, e.g., TEFOSE 63 (PEG-6 palmitostearate and ethylene glycol palmitostearate) or a similar product.

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., CAPMUL MCM) and polyethylene glycol glycerides (e.g., GELUCIRE) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65 C in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The progesterone can be added as the mixture cools, e.g., to below about 40 C or to below about 30 C, even down to room temperature.

In certain embodiments, an anionic and/or a non-ionic surfactant is used. Exemplary non-ionic surfactants may include one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as GELUCIRE, including, for example, GELUCIRE 44/11 and GELUCIRE 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, GELUCIRE 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, Tables below. Other non-ionic surfactants include, e.g., LABRASOL (Caprylocaproyl macrogol-8 glycerides EP Caprylocaproyl polyoxyl-8 glycerides NF PEG-8 Caprylic/Capric Glycerides (USA FDA IIG))(Gattefosse) and LABARAFIL (corn/apricot oil PEG-6 esters) (Gattefosse).

In various embodiments, a lubricant is used. Any suitable lubricant may be used, such as, for example and without limitation, lecithin, and in various embodiments, a mixture of polyethylene glycol ("PEG") esters, glycerides, and PEG, such as is commercially available under the trade name GELUCIRE (Gattefosse, FR) may also be used as a lubricant. Suitable lubricants may also comprise calcium stearate,

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ethyl oleate, ethyl laureate, glycerin, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium, oxide, magnesium stearate, poloxamer, glycols, and phospholipid mixtures. In particular, a mixture of polyethylene glycol esters, glycerides, and PEG such as GELUCIRE 44/14, may be used as a lubricant. GELUCIRE 44/14 is a non-ionic water dispersible surfactant, also known as lauroyl macrogol-32 glycerides EP and lauroyl polyoxyl-32 glycerides NF. In various embodiments, GELUCIRE 44/14 acts as a suspension agent.

In various embodiments, an antioxidant is used. Any suitable antioxidant may be used, such as, for example and without limitation, butylated hydroxytoluene. Butylated hydroxytoluene, a derivative of phenol, is lipophilic and is thus suited to being intermixed with ultra-micronized progesterone and carriers disclosed or contemplated herein.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises progesterone, at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of one or more glycols, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized.

Pharmaceutical formulations in accordance with various embodiments comprise ultra-micronized progesterone. In further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, a carrier, and a lubricant. In still further embodiments a pharmaceutical formulation comprises ultra-micronized progesterone, a carrier, a lubricant, and optionally an antioxidant. In still further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, and a medium chain triglyceride as a carrier. In still further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, and monoglycerides/diglycerides/triglycerides of caprylic/capric acid as a carrier. Various further embodiments also comprise lecithin and optionally butylated hydroxytoluene.

In additional embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone and at least one

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carrier, a lubricant, optionally an antioxidant, and other pharmaceutically acceptable excipients. For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

Formulations in accordance with various embodiments may be administered alone or combination with one or more other drugs (or as any combination thereof). For example, formulations in accordance with various embodiments may also comprise estradiol.

In various embodiments, ultra-micronized progesterone is administered in a capsule. Capsules may be prepared using one or more film forming polymers. Suitable film forming polymers include natural polymers, such as gelatin, and synthetic film forming polymers, such as modified celluloses. Suitable modified celluloses include, but are not limited to, hydroxypropyl methyl cellulose, methyl cellulose.

Hard or soft shell capsules can be used to administer the API. In certain embodiments, capsules may be prepared by forming the two capsule halves, filling one of the halves with the fill solution, and then sealing the capsule halves together to form the finished capsule.

Hard shell capsules may be prepared by combining the "Body" and the "Cap". The "Body" of the capsule is filled with the "fill mass" and then closed with the "Cap". The "Body"/"Cap" interface is then sealed/banded.

Soft gelatin capsules may be prepared using a rotary die encapsulation process, as further described below.

Suitable shell additives, for either a hard or soft shell capsules, may include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids, and combinations thereof. The main ingredients of the capsule shell is primarily gelatin (or a gelatin substitute for non-gelatin capsules), plasticizer, and purified water. Hard shell and soft shell capsules differ primarily in the amount of plasticizer present that is used in the capsule shell.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include, but are not limited to, glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light-sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to minimize cross-linking of the gelatin.

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In accordance with various embodiments, a softgel dosage form is used.

A softgel comprises two primary phases: a gel capsule and a fill material. The softgel may comprise a gelatin material in a relatively solid or stiff form. The softgel may define an inner volume that may contain the fill material. Dissolution of the softgel may commence at various points, such as along the digestive tract (mouth, esophagus, stomach and intestines), or other body cavities, such as the vaginal cavity.

As the softgel dissolves, the inner volume may come into fluid communication with the digestive system, allowing the fill material to leach outside the softgel. A softgel may also be punctured, cut, or otherwise opened outside a body. The fill material may then be poured or squeezed outside the gel capsule and applied on or in the body, such as within the vaginal cavity.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl esters (collectively known as "parabens") or combinations thereof.

The fill material may comprise a liquid, such as an oil, a solution, a suspension, or other acceptable forms. The active ingredient or active ingredient may be contained within the liquid.

Formulations in accordance with various embodiments may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Ultra-micronized progesterone in accordance with various embodiments may be formulated as a vaginal suppository or vaginal cream for administration onto the vulva or into the vagina, cervix, or uterus of a human. Capsules (e.g., softgels) containing ultra-micronized progesterone also may be administered vaginally, including insertion of a capsule directly into the vaginal cavity or delivery of such capsule contents into the vaginal cavity. Ultra-micronized progesterone, in accordance with various embodiments, may be formulated for intraperitoneal administration, and atomization, such as with nasal mist administration.

In accordance with various embodiments, enhanced bioavailability of progesterone is provided, such as over conventional progesterone formulations wherein it is well known that commercially available formulations of progesterone are poorly or inconsistently absorbed. While not bound by theory, the elements of the present formulation provide the enhanced performance characteristics as further described herein, including, for example and without limitation, improved bioavailability and the potential to be able to reduce the administered dosage strength compared to presently available progesterone formulations. Bioavailability comparisons to commercially available forms, such as tablet forms, may be determined by standard pharmacokinetic techniques.

In accordance with various embodiments, food effects are reduced, e.g., relative to comparative progesterone products.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

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Capsules may be arranged in blisters or cartridges or bottles.

According to various embodiments, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having delivery days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no API or hormone (e.g., progesterone) may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each dose (e.g., each softgel) may contain ultra-micronized progesterone in amounts of 100 mg, 150 mg, 200 mg, and 250 mg, though other dose ranges are contemplated herein. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Formulations in accordance with various embodiments may be used to treat or prevent preterm delivery in pregnant women, including in certain women having a shortened cervix. In various embodiments, a capsule, for example a softgel capsule, may be opened and the fill material applied in or around the vagina. However, in various embodiments the capsules are taken orally.

Formulations in accordance with various embodiments may be used to treat or prevent endometrial hyperplasia.

Formulations in accordance with various embodiments may be used to treat or prevent secondary amenorrhea.

Formulations in accordance with various embodiments may be used to mitigate or treat the effects of estradiol supplementation. In particular, formulations in accordance with various embodiments may be co-administered with estradiol and/or co-formulated with estradiol.

Formulations in accordance with various embodiments may be used to treat menopause-related symptoms, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy; and osteoporosis and endometrial hyperplasia reduction.

Additional objects of the present disclosure include: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

Specific Embodiments

Through extensive trial-and-error testing of various fatty acid esters of glycerol and other glycols, embodiments of the invention have been invented that have one or more favorable characteristics for development as a human drug product. Such favorable characteristics include those described above, e.g., improved PK and reduced variability.

Such embodiments include an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical

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ingredient, in micronized form suspended in a carrier that comprises a medium chain fatty acid-glycol ester or mixtures thereof and a non-ionic surfactant comprising a polyethylene glycol fatty acid ester.

A more specific such embodiment is such formulation wherein the progesterone is ultramicrosized.

In certain such embodiments, the progesterone is suspended and/or solubilized in one or more C6 to C12 fatty acid mono-, di-, or triesters of glycerol, e.g., one or more C6 to C14 triglycerides, e.g., one or more C6 to C12 triglycerides, such as one or more C8-C10 triglycerides. An example of a carrier that provides beneficial properties is C8, C10, or C8 and C10 saturated triglycerides, such as but not limited to MIGLYOL, e.g., MIGLYOL 812.

In such general and more specific embodiments, the non-ionic surfactant is a polyethylene glycol saturated or unsaturated fatty acid ester or diester. In certain such embodiments, the non-ionic surfactant comprises C8 to C18 fatty acid esters of glycerol and polyethylene glycol. An example of a non-ionic surfactant that provides beneficial properties is GELUCIRE, e.g., GELUCIRE 44/14.

In certain such embodiments, the non-ionic surfactant has a HLB value of about 15. An illustrative example of such surfactant is GELUCIRE 44/14.

As noted above, such formulations are liquid at room temperature, not gels, hard fats, or any other solid form. The non-ionic surfactant serves to increase viscosity. In some such embodiments, the non-ionic surfactant, e.g., GELUCIRE or TEFOSE, may be solid at room temperature and require melting to effect mixing with the estradiol solubilized in fatty acid-glycol esters but the resultant formulation is advantageously liquid, not solid.

The formulation of such embodiments is typically encapsulated in a soft gelatin capsule or other soft capsule.

Typically, such formulations do not comprise a bioadhesive (i.e., muco-adhesive) agent, a gelling agent, or a dispersing agent, or, at least, do not comprise one or two of such components.

In more specific such formulations, the capsule shell, the active pharmaceutical ingredient, the fatty acid esters and the non-ionic surfactant are the only essential ingredients. Non-essential ingredients, e.g., colorants, antioxidants or other preservatives, etc., may, of course, be included but other ingredients in amounts that would materially change the solubility of the progesterone, the PK of the encapsulated formulation, or other clinically relevant properties, e.g., other oils or fatty acid esters, lecithin, muco-adherent agents, gelling agents, dispersing agents, or the like would not be included. Such embodiments of the invention may be described as consisting essentially of the capsule shell, the active pharmaceutical ingredient, the fatty acid esters and the non-ionic surfactant, as described in the immediately preceding paragraphs describing illustrative embodiments discovered to have favorable characteristics.

As an example of such embodiments discovered to have such favorable characteristics is mentioned the product identified in Example 2, Table 3, below.

EXAMPLES

Example 1

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 2

Ingredient	mg/ Capsule	%	Function
Ultra-micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 2

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 3

Ingredient	%	mg/ Capsule	Function
1. Ultra-micronized Progesterone	30.77	200.00	Active
2. Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
3. Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	3.00	19.50	Suspending Agent
4. Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 3

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL, including without limitation MIGLYOL 812, may be used in embodiments comprising a suspension of progesterone.

As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

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Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg.

TABLE 4

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM	73.4
CAPMUL PG8	95
MIGLYOL 812	27.8
CAPMUL MCM: GELUCIRE 44/14 (9:1)	86.4
CAPMUL MCM: GELUCIRE 44/14 (7:3)	70.5
CAPMUL MCM: GELUCIRE 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM in combination with GELUCIRE 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM and GELUCIRE 44/14 system, wherein the ratio of CAPMUL MCM to GELUCIRE 44/14 is 9:1.

TABLE 5

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM:GELUCIRE 44/14 (9:1)	86.4
CAPMUL MCM:GELUCIRE 44/14 (7:3)	70.5
CAPMUL MCM:GELUCIRE 44/14 (6:4)	57.4

Example 4

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 6

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

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TABLE 7

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 8

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 6

Bioavailability Assessment—Fasted

A randomized single-dose oral bioequivalence study comparing 200 mg ultra-micronized progesterone capsule test product (T) and 200 mg PROMETRIUM® (progesterone) capsules (Abbott Laboratories, Abbott Park, Ill.) reference product (R) is conducted. Subjects are administered a single 200 mg dose of either test product (T) or the reference product (R) under fasting conditions, for example, subjects fasted at least 10.0 hours prior to dosing. Blood is collected pre-dose and post-dose. Pre-dose samples are collected at approximately -01.00, -00.50, and 00.00 hours. Post-dose samples are collected at approximately 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 09.00, 10.00, 12.00, 18.00, 24.00, 36.00 and 48.00 hours. Standard meals are provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00 and 37.00 hours post-dose.

Pharmacokinetic measurements are assessed including C_{max} , AUC and optionally T_{max} . Comparative bioavailability of the test product (T) and reference product are assessed.

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Example 7

Bioavailability Assessment—Fed

The procedures for determining bioavailability under fasted conditions are repeated except that subjects are administered a single 200 mg dose of either test product (T) or reference product (R) immediately following a high fat meal, for example, within 30 minutes of dosing. Blood is collected pre-dose and post-dose. Pre-dose samples are collected at approximately -01.00, -00.50, and 00.00 hours. Post-dose samples are collected at approximately 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 09.00, 10.00, 12.00, 18.00, 24.00, 36.00 and 48.00 hours. Standard meals are provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00 and 37.00 hours post-dose. Pharmacokinetic measurements are assessed including C_{max} , AUC and optionally T_{max} . Bioavailability of the test product (T) in reference to the reference product is assessed. The effect of food on the comparative bioavailability of the test product (T) and the reference product (R) are also assessed.

Example 8

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material, i.e. fill mass, preparation 100 is shown. Step 102 comprises mixing a carrier, a lubricant, and an antioxidant as described herein. For example, lecithin and butylated hydroxytoluene may be mixed with one or more medium chain mono-, di- or triglycerides, or combinations thereof mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 104 may comprise mixing ultra-micronized progesterone into the mixture of the carrier, the lubricant, and the antioxidant. A pasty substance is thus formed. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 104 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 106 comprises degassing. The resulting mixture from step 106 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Heating may be performed until the temperature reaches $80^{\circ}\pm 5^{\circ}$ C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 208 comprises degassing. The resulting mixture from step 208 may comprise

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a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C./ $\pm 3^{\circ}$ C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C./ $\pm 10^{\circ}$ C. The wedge temperature may be 38° C./ $\pm 3^{\circ}$ C. The drum cooling temperature may be 4° C./ $\pm 2^{\circ}$ C. The encapsulator may be lubricated using MIGLYOL 812. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 ± 0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight $\pm 5\%$ (i.e., 650 ± 33 mg and 325 ± 16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Polishing may be performed with isopropyl alcohol.

Example 9

Stability Study

In accordance with various embodiments, formulations in accordance with various embodiments have an exemplary shelf life of 3 months with storage at $25\pm 2^{\circ}$ C./ $60\pm 5\%$ RH in 75 cc HDPE white, opaque bottles with a 38/400 mm white child resistant cap.

Packaging during testing comprises a 75 cc round HDPE bottle and 33 mm cap. A Brasken FPT 300F resin is associated with the cap. Testing criteria include visual appearance, assay of progesterone, dissolution, content uniformity and microbial limits testing.

Three test groups are created. Test group 1 comprises a test at 40° C./75% RH. Test group 2 comprises a test at 30° C./65% RH. Test group 3 comprises a test at 25° C./60% RH. Test group 1 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 1, 2, 3, and 6. Test group 2 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 0, 1, 2, 3, 6, and 12. Test group 3 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 0, 1, 2, 3, 6, 12 and 24.

Example 10

A particle size analysis is conducted by using a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device"). The Beckman Device uses laser diffraction to determine particle size. A sample of a formulation in accordance with various embodiments is provided. The Beckman Device particle sensor yields that the sample has an X50 of 6.67 μ m, an X75 of 14.78 μ m, and an X25 of 2.193 μ m.

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Example 11

A dissolution study was performed using a formulation in accordance with various embodiments. The results of the dissolution study are shown in FIG. 4.

The dissolution study was performed using a United States Pharmacopoeia dissolution apparatus 3 (reciprocating cylinder) ("USP Apparatus 3"). The USP Apparatus 3 was set to 30 dips per minute. Two hundred fifty mL (250 mL) of a solution of 1N HCL with 3% sodium lauryl sulfate was used at 37° C.

FIG. 4 shows dissolution percentage in the y axis over time in minutes on the x axis. A formulation in accordance with various embodiments is shown having circular dots, and is labeled formulation 402. An existing commercial pharmaceutical product containing progesterone is shown having square dots and is labeled existing product 404. As shown in FIG. 4, formulation 402 reaches a higher level of dissolution in a shorter time than existing product 404.

Example 12

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 5.

Example 13

Study 352—Progesterone and Estradiol Combination Study under Fed Conditions. This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	7.14	50.00
Estradiol Hemihydrate, USP Micronized	0.30	2.07
CAPMUL MCM, NF, USP	83.27	582.93
GELUCIRE 44/14, NF	9.29	650
Total	100.00	700

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The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted to at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of

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heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of $-70^{\circ}\text{C} \pm 20^{\circ}\text{C}$ in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters C_{\max} , AUC_{0-t} & $AUC_{0-\infty}$ were calculated on data obtained from 24 subjects for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 9, below, for progesterone.

TABLE 9

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean \pm Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C_{\max}	47.0	43.0	81.0 ± 82.8	117.7 ± 173.7
AUC_{0-t}	107.6	97.8	163.9 ± 136.5	191.1 ± 241.7
$AUC_{0-\infty}$	110.7	110.0	173.5 ± 143.0	207.1 ± 250.3

*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters C_{\max} , AUC_{0-t} & $AUC_{0-\infty}$ were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 10, below for progesterone.

TABLE 10

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean \pm Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C_{\max}	2.3	3.0	2.9 ± 2.3	3.9 ± 3.4
AUC_{0-t}	8.4	10.9	11.2 ± 8.7	14.5 ± 11.0
$AUC_{0-\infty}$	12.9	17.2	15.1 ± 9.0	19.6 ± 10.2

*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to PROMETRIUM.

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Example 14

Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of PROMETRIUM and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37 C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from PROMETRIUM. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from PROMETRIUM is attached as FIG. 6.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. The disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad, general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

What is claimed is:

1. A pharmaceutical composition comprising: progesterone;

a medium chain oil; and a non-ionic surfactant;

wherein the progesterone is present from about 20 to about 50 weight percent of the composition.

2. The pharmaceutical composition of claim 1, wherein the progesterone is ultra-micronized and has an X50 less than or equal to 15 microns.

3. The pharmaceutical composition of claim 2, wherein the ultra-micronized progesterone has an X90 of less than about 25 microns.

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4. The pharmaceutical composition of claim 1, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.

5. The pharmaceutical composition of claim 1, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.

6. The pharmaceutical composition of claim 1, wherein the composition is provided in a gelatin capsule.

7. The pharmaceutical composition of claim 1, wherein the composition provides increased bioavailability compared to a micronized progesterone suspended in peanut oil.

8. The pharmaceutical composition of claim 1, wherein progesterone is the sole active ingredient.

9. The pharmaceutical composition of claim 1, wherein the medium chain oil comprises at least one C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.

10. The pharmaceutical composition of claim 9, wherein the at least one C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol is a C₈ fatty acid mono-, di-, or tri-ester of glycerol.

11. The pharmaceutical composition of claim 10, further comprising a second C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol.

12. The pharmaceutical composition of claim 11, wherein the second C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol is a C₁₀ fatty acid mono-, di-, or tri-ester of glycerol.

13. The pharmaceutical composition of claim 12, wherein the medium chain oil is MIGLYOL 812.

14. A pharmaceutical composition comprising:

75 mg of progesterone;

a medium chain oil; and

a non-ionic surfactant;

wherein the progesterone is present at from about 20 to about 50 weight percent of the composition.

15. The pharmaceutical composition of claim 14, wherein the progesterone is ultra-micronized and has an X50 less than or equal to 15 microns.

16. The pharmaceutical composition of claim 15, wherein the ultra-micronized progesterone has an X90 of less than about 25 microns.

17. The pharmaceutical composition of claim 14, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.

18. The pharmaceutical composition of claim 14, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.

19. The pharmaceutical composition of claim 14, wherein the composition is provided in a gelatin capsule.

20. The pharmaceutical composition of claim 14, wherein the composition provides increased bioavailability compared to a micronized progesterone suspended in peanut oil.

21. The pharmaceutical composition of claim 14, wherein progesterone is the sole active ingredient.

22. The pharmaceutical composition of claim 14, wherein the medium chain oil comprises at least one C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.

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23. The pharmaceutical composition of claim 22, wherein the at least one C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol is a C₈ fatty acid mono-, di-, or tri-ester of glycerol.

24. The pharmaceutical composition of claim 23, further comprising a second C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol.

25. The pharmaceutical composition of claim 24, wherein the second C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol is a C₁₀ fatty acid mono-, di-, or tri-ester of glycerol.

26. The pharmaceutical composition of claim 25, wherein the medium chain oil is MIGLYOL 812.

27. A pharmaceutical composition comprising:

150 mg progesterone;

a medium chain oil; and

a non-ionic surfactant;

wherein the progesterone is present at from about 20 to about 50 weight percent of the composition.

28. The pharmaceutical composition of claim 27, wherein the progesterone is ultra-micronized and has an X50 less than or equal to 15 microns.

29. The pharmaceutical composition of claim 28, wherein the ultra-micronized progesterone has an X90 of less than about 25 microns.

30. The pharmaceutical composition of claim 27, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.

31. The pharmaceutical composition of claim 27, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.

32. The pharmaceutical composition of claim 27, wherein the composition is provided in a gelatin capsule.

33. The pharmaceutical composition of claim 27, wherein the composition provides increased bioavailability compared to a micronized progesterone suspended in peanut oil.

34. The pharmaceutical composition of claim 27, wherein progesterone is the sole active ingredient.

35. The pharmaceutical composition of claim 27, wherein the medium chain oil comprises at least one C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.

36. The pharmaceutical composition of claim 35, wherein the at least one C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol is a C₈ fatty acid mono-, di-, or tri-ester of glycerol.

37. The pharmaceutical composition of claim 36, further comprising a second C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol.

38. The pharmaceutical composition of claim 37, wherein the second C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol is a C₁₀ fatty acid mono-, di-, or tri-ester of glycerol.

39. The pharmaceutical composition of claim 38, wherein the medium chain oil is MIGLYOL 812.

40. The pharmaceutical composition of claim 27, wherein the medium chain oil is MIGLYOL 812, the non-ionic surfactant is lauroyl polyoxyl-32-glycerides, and wherein the pharmaceutical formulation provides increased progesterone bioavailability compared to a formulation comprising an equivalent amount of micronized progesterone suspended in peanut oil.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 10,052,386 B2
APPLICATION NO. : 14/125547
DATED : August 21, 2018
INVENTOR(S) : Bernick et al.

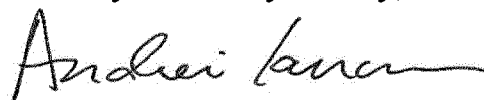
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

In Column 10, Line 31, replace "PEG-6-palmitostearate" with -- PEG-6 stearate --.

Signed and Sealed this
Twenty-third Day of July, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu", written in a cursive style.

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT L



US010206932B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 10,206,932 B2**

(45) **Date of Patent:** ***Feb. 19, 2019**

- (54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**
- (71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)
- (72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US); **Peter H. R. Persicaner**, Boca Raton, FL (US); **Julia M. Amadio**, Boca Raton, FL (US)
- (73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 78 days.
This patent is subject to a terminal disclaimer.
- (21) Appl. No.: **14/719,933**
- (22) Filed: **May 22, 2015**
- (65) **Prior Publication Data**
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Related U.S. Application Data

- (60) Provisional application No. 62/002,090, filed on May 22, 2014.

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- (51) **Int. Cl.**
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A61K 31/57 (2006.01)
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- (52) **U.S. Cl.**
CPC **A61K 31/565** (2013.01); **A61K 9/10** (2013.01); **A61K 9/4858** (2013.01); **A61K 31/57** (2013.01)

- (58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — Jared Barsky

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton LLP

(57) **ABSTRACT**

Pharmaceutical compositions for co-administering estradiol and progesterone to a human subject in need thereof are provided. In some embodiments, the pharmaceutical composition comprises solubilized estradiol, suspended progesterone, and a solubilizing agent comprising a medium chain (C6-C12) oil.

20 Claims, 4 Drawing Sheets

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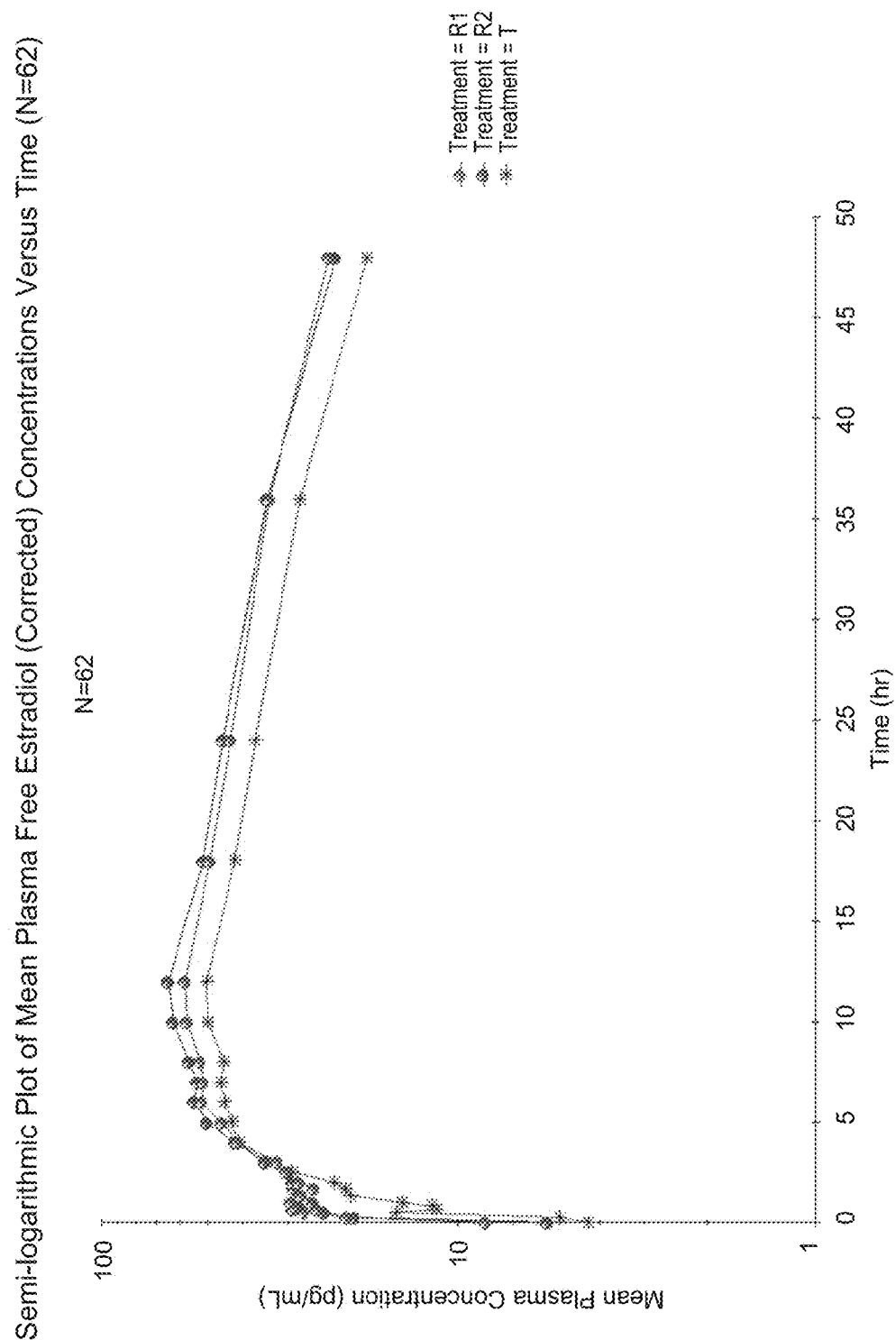


FIG. 1

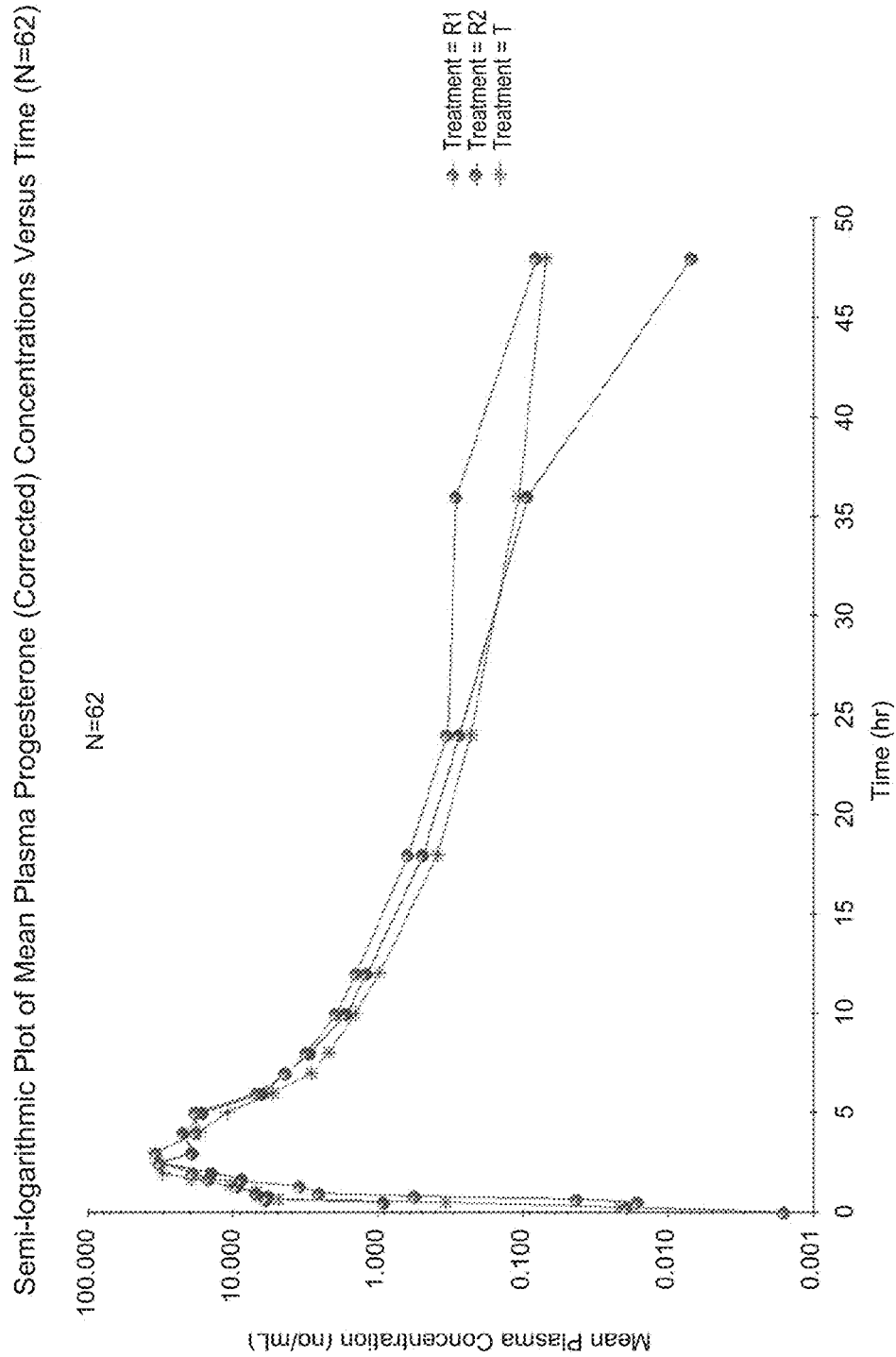


FIG. 2

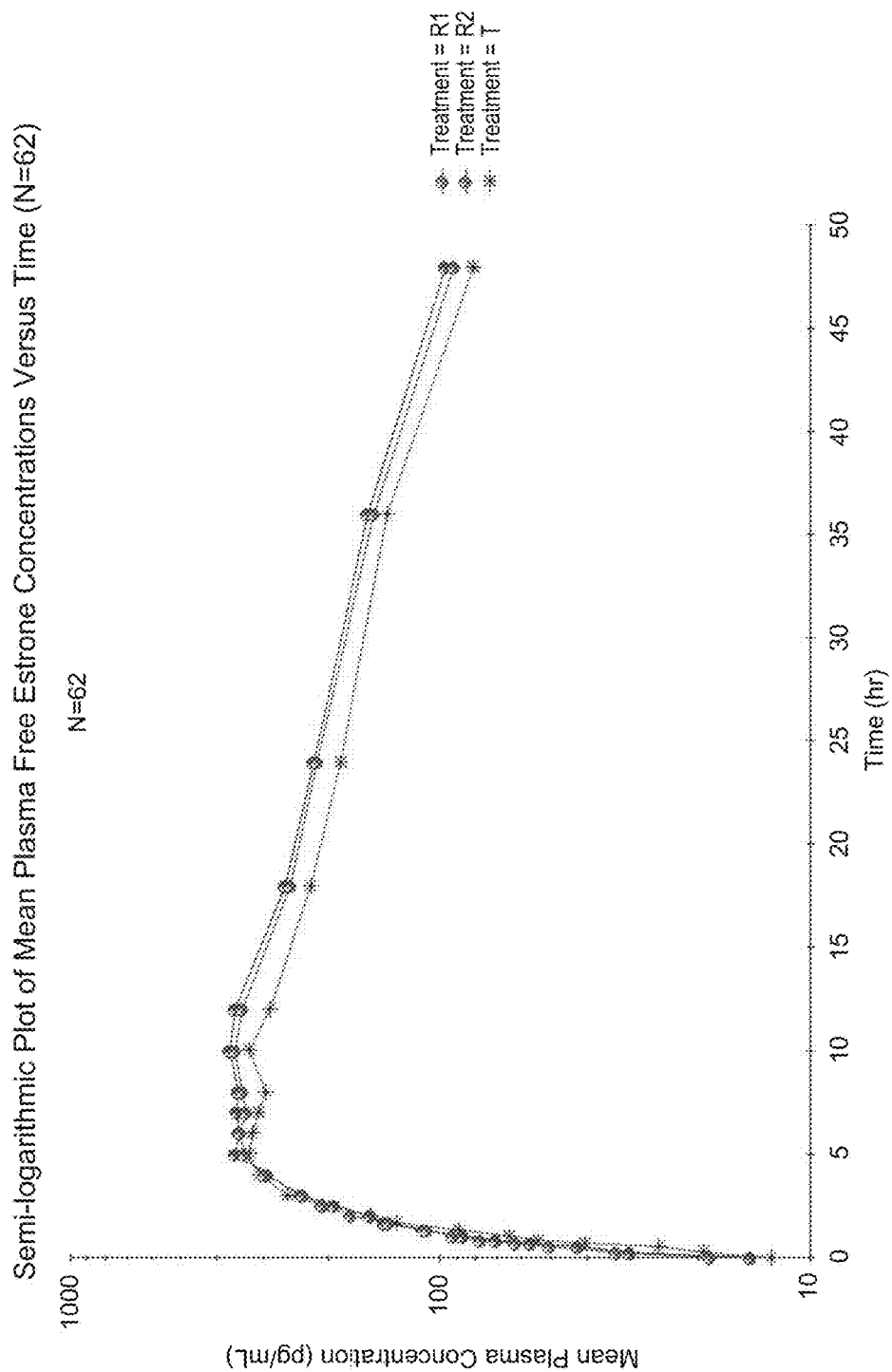


FIG. 3

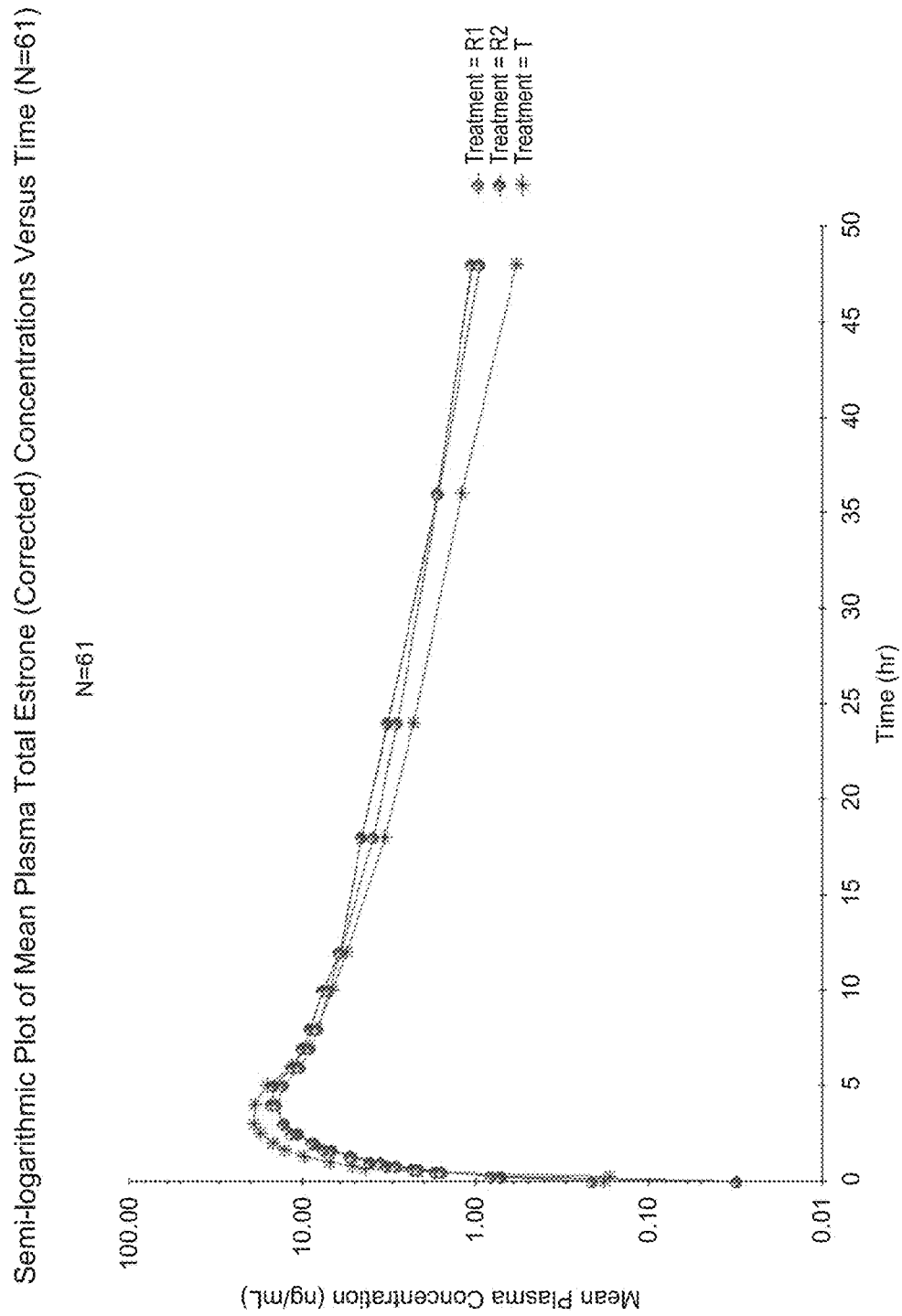


FIG. 4

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NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Ser. No. 62/002,090, filed May 22, 2014, the content of which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

This application relates to pharmaceutical compositions and methods for hormone replacement therapy.

BACKGROUND OF THE INVENTION

Hormone Replacement Therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones in a pre-menopausal, peri-menopausal, menopausal or post-menopausal subject.

BRIEF SUMMARY OF THE INVENTION

In one aspect, pharmaceutical compositions for co-administering estradiol and progesterone to a subject in need of natural hormone replacement therapies are provided. In some embodiments, the pharmaceutical composition comprises: solubilized estradiol, suspended progesterone, and a solubilizing agent, wherein the solubilizing agent is a medium chain (C6-C12) oil and wherein the pharmaceutical composition, when administered to a subject, produces in a plasma sample from the subject one or more pharmacokinetic parameters as described herein (e.g., an area under the curve ($AUC_{(0-t)}$) or a C_{max} for estradiol, progesterone, estrone, or total estrone as described herein, e.g., in Tables 18-21).

In some embodiments, the pharmaceutical composition comprises a solubilizing agent that comprises a glyceride of at least one C6-C12 fatty acid. In some embodiments, the glyceride ester is a mixture of mono- and diglycerides (e.g., glyceryl caprylate/caprate). In some embodiments, the fatty acid is predominantly a C8 to C10 fatty acid. In some embodiments, the pharmaceutical composition further comprises a surfactant (e.g., lauroyl polyoxyglyceride). In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprises progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.25 mg and comprises progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.50 mg and comprises progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.50 mg and comprises progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 1 mg and comprises progesterone at a dosage of about 100 mg. In some embodi-

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ments, the pharmaceutical composition comprises estradiol at a dosage of about 2 mg and comprises progesterone at a dosage of about 200 mg.

In some embodiments, the pharmaceutical composition comprises about 0.25 mg estradiol and about 50 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; and a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml.

In some embodiments, administration of the composition to subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; and a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.25 mg estradiol and about 50 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml and (b) a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml and (b) a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 0.50 mg estradiol and about 50 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$

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for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, and a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.50 mg estradiol and about 50 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $UC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 0.50 mg estradiol and about 100 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, and a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.50 mg estradiol and about 100 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a

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C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally

- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 1 mg estradiol and about 100 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml, and a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml, and a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.50 mg estradiol and about 100 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml and (b) a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml and (b) a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In some embodiments, the pharmaceutical composition has the blood plasma estradiol concentration profile of FIG. 1. In some embodiments, the pharmaceutical composition has the blood plasma progesterone concentration profile of FIG. 2. In some embodiments, the pharmaceutical composition has the blood plasma estrone concentration profile of FIG. 3. In some embodiments, the pharmaceutical composition has the blood plasma total estrone concentration profile of FIG. 4.

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In some embodiments, the one or more parameters as described herein (e.g., the $AUC_{(0-t)}$ or C_{max} for progesterone, estradiol, estrone, or total estrone) are measured at regular intervals (e.g., about every 30 minutes, about every 60 minutes, or about every 90 minutes) or at irregular intervals over a period of time such as 24 hours or 48 hours. In some embodiments, the one or more parameters as described herein (e.g., the $AUC_{(0-t)}$ or C_{max} for progesterone, estradiol, estrone, or total estrone) are measured at about 0.25 hr, 0.5 hr, 0.67 hr, 0.83 hr, 1 hr, 1.33 hr, 1.67 hr, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr, 10 hr, 12 hr, 18 hr, 24 hr, 36 hr, or 48 hr after administering the pharmaceutical composition to the subject. In some embodiments, the one or more parameters as described herein are measured at regular or irregular intervals following the administration of a single dose or of a first dose of the pharmaceutical composition to the subject.

In another aspect, methods of treating a subject are provided. In some embodiments, the subject has a condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause, such as vasomotor symptoms). In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent that comprises a medium chain (C6-C12) oil as described herein, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more pharmacokinetic parameters as described herein. In some embodiments, the method comprises administering a pharmaceutical composition comprising estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprising progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg. In some embodiments, the method comprises administering a pharmaceutical composition comprising: estradiol at a dosage of about 0.25 mg and progesterone at a dosage of about 50 mg; estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 50 mg; estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 100 mg; estradiol at a dosage of about 1 mg and progesterone at a dosage of about 100 mg; or estradiol at a dosage of about 2 mg and progesterone at a dosage of about 200 mg.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the pharmaceutical composition further produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; and a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

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In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml and (b) a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml and (b) a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

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In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml; a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml; and a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

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In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml and (b) a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml and (b) a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In still another aspect, pharmaceutical compositions for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency are provided. In some embodiments, the pharmaceutical composition comprises solubilized estradiol, suspended progesterone, and a solubilizing agent that comprises a medium chain (C6-C12) oil, wherein the treatment produces, in a plasma sample from the subject, one or more pharmacokinetic parameters as described herein (e.g., an $AUC_{(0-t)}$ or C_{max} for estradiol, progesterone, estrone, or total estrone as described herein, e.g., as described in any of Tables 18-21). In some embodiments, the pharmaceutical compositions for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency comprise estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprise progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg.

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 0.25 mg and progesterone at a dosage of about 50 mg, and produces one or more pharmacokinetic values disclosed in Table 18 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 50 mg, and produces one or more pharmacokinetic values disclosed in Table 19 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 100 mg, and produces one or more pharmacokinetic values disclosed in Table 20 following administration of a

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single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 1 mg and progesterone at a dosage of about 100 mg, and produces one or more pharmacokinetic values disclosed in Table 21 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates a semilogarithmic plot of mean plasma concentration (pg/ml) over time (hrs) for estradiol.

FIG. 2 illustrates a semilogarithmic plot of mean plasma concentration (ng/ml) over time (hrs) for progesterone.

FIG. 3 illustrates a semilogarithmic plot of mean plasma concentration (pg/ml) over time (hrs) for estrone.

FIG. 4 illustrates a semilogarithmic plot of mean plasma concentration (ng/ml) over time (hrs) for total estrone.

DETAILED DESCRIPTION OF THE INVENTION

In the following detailed description of embodiments of this disclosure, reference is made to the accompanying drawings in which like references indicate similar elements, and in which is shown, by way of illustration, specific embodiments in which this disclosure may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice this disclosure, and it is to be understood that other embodiments may be utilized and that other changes may be made without departing from the scope of this disclosure. The following detailed description is, therefore, not to be taken in a limiting sense, and the scope of this disclosure is defined only by the appended claims. As used in this disclosure, the term “or” shall be understood to be defined as a logical disjunction (i.e., and/or) and shall not indicate an exclusive disjunction unless expressly indicated as such with the term “either,” “unless,” “alternatively,” and words of similar effect.

I. DEFINITIONS

The term “area under the curve” (“AUC”) refers to the area under the curve defined by changes in the blood, plasma, or serum concentration of an active pharmaceutical ingredient (e.g., estradiol or progesterone), or one or more metabolites of the active pharmaceutical ingredient, over time following the administration of a dose of the active pharmaceutical ingredient. “AUC_{0-∞}” is the area under the concentration-time curve extrapolated to infinity following the administration of a dose. “AUC_{0-t}” is the area under the concentration-time curve from time zero to time t following the administration of a dose, wherein t is the last time point with measurable concentration.

The term “C_{max}” refers to the maximum value of blood, plasma, or serum concentration shown on the curve that represents changes in blood, plasma, or serum concentrations of an active pharmaceutical ingredient (e.g., progesterone or estradiol), or one or more metabolites of the active pharmaceutical ingredient, over time.

The term “T_{max}” refers to the time that it takes for the blood, plasma, or serum concentration of an active pharma-

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ceutical ingredient (e.g., estradiol or progesterone), or of one or more metabolites of the active pharmaceutical ingredient, to reach the maximum value.

Collectively, AUC, C_{max}, and, optionally, T_{max} are the principal pharmacokinetic parameters that can characterize the pharmacokinetic response of a particular drug product, such as progesterone or estradiol, in an animal, especially a mammal, including human, subject.

An “active pharmaceutical ingredient” (API), as used herein, means the active compound or compounds used in formulating a drug product. APIs are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “bioavailability” has the meaning as defined in 21 C.F.R. § 320.1(a): the rate and extent to which an API or active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the API or active ingredient or active moiety becomes available at the site of action. For example, bioavailability can be measured as the amount of API in the blood (whole blood, serum, or plasma) as a function of time. In embodiments, the amount of API is measured in blood plasma. Pharmacokinetic (PK) parameters such as AUC, C_{max}, or T_{max} may be used to measure and assess bioavailability.

The term “bioequivalent” has the meaning as defined in 21 C.F.R. § 320.1(e): the absence of a significant difference in the rate and extent to which the API or active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended release dosage forms or modified release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. In practice, two products are considered bioequivalent if the 90% confidence interval of the AUC, C_{max}, or optionally T_{max} is within 80.00% to 125.00%.

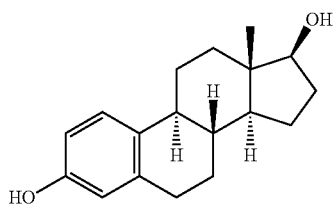
The term “bio-identical hormone” or “body-identical hormone” refers to an active pharmaceutical ingredient that is structurally identical to a hormone naturally or endogenously found in the human body (e.g., estradiol and progesterone).

The term “estrogen” refers to a group of several female sex hormones produced primarily by the ovaries, including estradiol, estrone, and estrinol. As used herein, unless otherwise specified, estrogen refers to estradiol.

The term “estradiol” refers to (17β)-estra-1,3,5(10)-triene-3,17-diol. Estradiol is also interchangeably called 17β-estradiol, oestradiol, or E2, and is found endogenously in the human body. As used herein, estradiol refers to the bio-identical or body-identical form of estradiol found in the human body having the structure:

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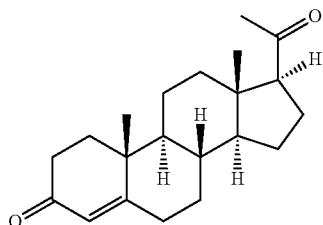
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As used herein, unless specified, estradiol includes estradiol in anhydrous or hemi-hydrate forms. For the purposes of this disclosure, the anhydrous form or the hemihydrate form can be substituted for the other by accounting for the water or lack of water according to well-known and understood techniques.

The term “solubilized estradiol” means that the estradiol or a portion thereof is solubilized or dissolved in the solubilizing agents or the formulations disclosed herein. Solubilized estradiol may include estradiol that is about 80% solubilized, about 85% solubilized, about 90% solubilized, about 95% solubilized, about 96% solubilized, about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. In some embodiments, the estradiol is “fully solubilized” with all or substantially all of the estradiol being solubilized or dissolved in the solubilizing agent. Fully solubilized estradiol may include estradiol that is about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. Solubility can be expressed as a mass fraction (% w/w, which is also referred to as wt %).

The term “progesterone” refers to pregn-4-ene-3,20-dione. Progesterone is also interchangeably called P4 and is found endogenously in the human body. As used herein, progesterone refers to the bio-identical or body-identical form of progesterone found in the human body having the structure:



The term “solubilized progesterone” means that the progesterone or a portion thereof is solubilized or dissolved in the solubilizing agents or the formulations disclosed herein. In some embodiments, the progesterone is “partially solubilized” with a portion of the progesterone being solubilized or dissolved in the solubilizing agent and a portion of the progesterone being suspended in the solubilizing agent. Partially solubilized progesterone may include progesterone that is about 1% solubilized, about 5% solubilized, about 10% solubilized, about 15% solubilized, about 20% solubilized, about 30% solubilized, about 40% solubilized, about 50% solubilized, about 60% solubilized, about 70% solubilized, about 80% solubilized, about 85% solubilized, about 90% solubilized or about 95% solubilized. In other embodiments, the progesterone is “fully solubilized” with all or substantially all of the progesterone being solubilized or dissolved in the solubilizing agent. Fully solubilized progesterone may include progesterone

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that is about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. Solubility can be expressed as a mass fraction (% w/w, which is also referred to as wt %).

The terms “micronized progesterone” and “micronized estradiol,” as used herein, include micronized progesterone and micronized estradiol, respectively, having an X50 particle size value below about 15 microns or having an X90 particle size value below about 25 microns. The term “X50” means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “solubilizing agent” refers to an agent or combination of agents that solubilize an active pharmaceutical ingredient (e.g., estradiol or progesterone). For example and without limitation, suitable solubilizing agents include medium chain oils and other solvents and co-solvents that solubilize or dissolve an active pharmaceutical ingredient to a desirable extent. Solubilizing agents suitable for use in the formulations disclosed herein are pharmaceutical grade solubilizing agents (e.g., pharmaceutical grade medium chain oils). It will be understood by those of skill in the art that other excipients or components can be added to or mixed with the solubilizing agent to enhance the properties or performance of the solubilizing agent or resulting formulation. Examples of such excipients include, but are not limited to, surfactants, emulsifiers, thickeners, colorants, flavoring agents, etc. In some embodiments, the solubilizing agent is a medium chain oil and, in some other embodiments, the medium chain oil is combined with a co-solvent(s) or other excipient(s).

The term “medium chain” is used to describe the aliphatic chain length of fatty acid containing molecules. “Medium chain” specifically refers to fatty acids, fatty acid esters, or fatty acid derivatives that contain fatty acid aliphatic tails or carbon chains that contain between 6 (C6) and 14 (C14) carbon atoms.

The terms “medium chain fatty acid” and “medium chain fatty acid derivative” are used to describe fatty acids or fatty acid derivatives with aliphatic tails (i.e., carbon chains) having 6 to 14 carbons. Fatty acids consist of an unbranched aliphatic tail attached to a carboxylic acid functional group. Fatty acid derivatives include, for example, fatty acid esters and fatty acid containing molecules, including, without limitation, mono-, di- and triglycerides that include components derived from fatty acids as well as fatty acid esters of ethylene or propylene glycol. Those of skill will appreciate that the aliphatic tails can be saturated or unsaturated (one or more double bonds between carbon atoms). In some embodiments, the aliphatic tails are saturated (i.e., no double bonds between carbon atoms). Medium chain fatty acids or medium chain fatty acid derivatives include those with aliphatic tails having 6-14 carbons, including those that are C6-C14, C6-C12, C8-C14, C8-C12, C6-C10, C8-C10, or others. In embodiments, medium chain fatty acids or medium chain fatty acid derivatives are those that are saturated. Examples include, without limitation, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, and derivatives thereof.

The term “oil,” as used herein, refers to any pharmaceutically acceptable oil, and specifically excluding peanut oil, that can suspend or solubilize any suitable progesterone or

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estradiol, starting material, or precursor, including micronized progesterone or estradiol as described herein.

The term “medium chain oil” refers to an oil wherein the composition of the fatty acid fraction of the oil is substantially medium chain (i.e., C6 to C14) fatty acids, i.e., the composition profile of fatty acids in the oil is substantially medium chain. As used herein, “substantially” means that between 20% and 100% (inclusive of the upper and lower limits) of the fatty acid fraction of the oil is made up of medium chain fatty acids, i.e., fatty acids with aliphatic tails (i.e., carbon chains) having 6 to 14 carbons. In some embodiments, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 85%, about 90% or about 95% of the fatty acid fraction of the oil is made up of medium chain fatty acids. Those of skill in the art that will readily appreciate that the terms “alkyl content” or “alkyl distribution” of an oil can be used in place of the term “fatty acid fraction” of an oil in characterizing a given oil or solubilizing agent, and these terms are used interchangeable herein. As such, medium chain oils suitable for use in the formulations disclosed herein include medium chain oils wherein the fatty acid fraction of the oil is substantially medium chain fatty acids, or medium chain oils wherein the alkyl content or alkyl distribution of the oil is substantially medium chain alkyls (C6-C12 alkyls). It will be understood by those of skill in the art that the medium chain oils suitable for use in the formulations disclosed herein are pharmaceutical grade (e.g., pharmaceutical grade medium chain oils). Examples of medium chain oils include, for example and without limitation, medium chain fatty acids, medium chain fatty acid esters of glycerol (e.g., for example, mono-, di-, and triglycerides), medium chain fatty acid esters of propylene glycol, medium chain fatty acid derivatives of polyethylene glycol, and combinations thereof.

The term “ECN” or “equivalent carbon number” means the sum of the number of carbon atoms in the fatty acid chains of an oil, and can be used to characterize an oil as, for example, a medium chain oil or a long-chain oil. For example, tripalmitin (tripalmitic glycerol), which is a simple triglyceride containing three fatty acid chains of 16 carbon atoms, has an ECN of $3 \times 16 = 48$. Conversely, a triglyceride with an ECN=40 may have “mixed” fatty acid chain lengths of 8, 16, and 16; 10, 14, and 16; 8, 14, and 18; etc. Naturally occurring oils are frequently “mixed” with respect to specific fatty acids, but tend not to contain both long chain fatty acids and medium chain fatty acids in the same glycerol backbone. Thus, triglycerides with ECNs of 21-42 typically contain predominantly medium chain fatty acids; while triglycerides with ECNs of greater than 43 typically contain predominantly long chain fatty acids. For example, the ECN of corn oil triglyceride in the US Pharmacopeia (USP) would be in the range of 51-54. Medium chain diglycerides with ECNs of 12-28 will often contain predominantly medium chain fatty acids, while diglycerides with ECNs of 32 or greater will typically contain predominantly long chain fatty acids. Monoglycerides will have an ECN that matches the chain length of the sole fatty acid chain. Thus, monoglyceride ECNs in the range of 6-14 contain mainly medium chain fatty acids, and monoglycerides with ECNs 16 or greater will contain mainly long chain fatty acids.

The average ECN of a medium chain triglyceride oil is typically 21-42. For example, as listed in the USP, medium chain triglycerides have the following composition as the exemplary oil set forth in the table below:

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Fatty Acid Tail Length	% of Oil	Exemplary Oil
6	≤2.0	2.0
8	50.0-80.0	70.0
10	20.0-50.0	25.0
12	≤3.0	2.0
14	≤1.0	1.0

and would have an average ECN of $3 \times [(6 \times 0.02) + (8 \times 0.070) + (10 \times 0.25) + (12 \times 0.02) + (14 \times 0.01)] = 25.8$. The ECN of the exemplary medium chain triglycerides oil can also be expressed as a range (per the ranges set forth in the USP) of 24.9-27.0. For oils that have mixed mono-, di-, and triglycerides, or single and double fatty acid glycols, the ECN of the entire oil can be determined by calculating the ECN of each individual component (e.g., C8 monoglycerides, C8 diglycerides, C10 monoglycerides, and C10 diglycerides) and taking the sum of the relative percentage of the component multiplied by the ECN normalized to a monoglyceride for each component. For example, the oil having C8 and C10 mono- and diglycerides shown in the table below has an ECN of 8.3, and is thus a medium chain oil:

Fatty Acid Chain Length	% of Oil	ECN as % of Oil [(chain length) × (% in oil)]	ECN as % of Oil Normalized to Monoglyceride
C8 monoglyceride	47	$8 \times 0.47 = 3.76$	3.76
C10 monoglyceride	8	$10 \times 0.08 = 0.8$	0.8
C8 diglyceride	38	$2 \times (8 \times 0.38) = 6.08$	$6.08/2 = 3.04$
C10 diglyceride	7	$2 \times (10 \times 0.07) = 1.4$	$1.4/2 = 0.7$
OIL ECN (normalized to monoglycerides)			8.3

Expressed differently, ECN can be calculated as each chain length in the composition multiplied by its relative percentage in the oil: $(8 \times 0.85) + (10 \times 0.15) = 8.3$.

The term “excipients,” as used herein, refers to non-active pharmaceutical ingredients such as solubilizing agents, antioxidants, oils, lubricants, and others used in formulating pharmaceutical products.

The terms “treat,” “treating,” and “treatment” refer to any indicia of success in the treatment or amelioration of an injury, disease, or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, disease, or condition more tolerable to the patient; slowing in the rate of degeneration or decline; or improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subject parameters, including the results of a physical examination, neuropsychiatric examinations, or psychiatric evaluation.

II. PHARMACEUTICAL COMPOSITIONS

In one aspect, this disclosure relates to pharmaceutical compositions for co-administering estradiol and progesterone to a human subject in need thereof. In some embodiments, the composition comprises estradiol, progesterone, and a solubilizing agent (e.g., a medium chain oil, e.g., a C6-C12 oil). In some embodiments, a pharmaceutical composition comprising estradiol, progesterone, and a solubilizing agent as described herein, when administered to a subject or a population of subjects, produces one or more AUC, C_{max} , or T_{max} parameters for estradiol, progesterone, estrone, or total estrone as described below.

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Formulations of Estradiol and Progesterone Compositions

In some embodiments, a pharmaceutical composition for use as described herein comprises solubilized estradiol with suspended progesterone; solubilized estradiol with both partially solubilized progesterone and partially suspended progesterone; or solubilized estradiol with fully solubilized progesterone. In some embodiments, the composition comprises solubilized estradiol and suspended progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone, although the natural or bio-identical forms of estradiol and progesterone are preferred.

In some embodiments, the composition comprises estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg. In some embodiments, the composition comprises progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg.

In some embodiments, estradiol is solubilized. Solubilized estradiol may include estradiol that is approximately 80% to 100% soluble in a solubilizing agent, including specifically embodiments that are: 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% soluble in a solubilizing agent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %). In some embodiments, estradiol is micronized. In some embodiments, micronized estradiol has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns or less than about 3 microns. In some embodiments, micronized estradiol has an X90 particle size value of less than about 25 microns, less than about 20 microns, or less than about 15 microns. In some embodiments, the composition comprises micronized and partially solubilized estradiol.

In some embodiments, the composition comprises micronized progesterone. The progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, or less than about 15 microns. Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size.

Estradiol and progesterone compositions and methods of preparing such compositions are described in U.S. Pat. No. 8,633,178; U.S. Publication No. 2013/0129818; U.S. Publication No. 2013/0338123; International Publication No. WO 2013/078422; and International Publication No. WO 2013/192251; each of which is incorporated by reference in its entirety.

Solubilizing Agents

Estradiol and progesterone compositions of the present disclosure are prepared via blending with a solubilizing agent. In some embodiments, the solubilizing agent is a pharmaceutically acceptable oil that comprises a medium chain oil. In some embodiments, the solubilizing agent is a medium chain oil comprised substantially of C6-C12 medium chains, e.g., at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at

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least 90% of the chains present in the oil are C6-C12. In some embodiments, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids having at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. In some embodiments, the medium chain oil comprises at least one medium chain fatty acid or propylene glycol, polyethylene glycol, or glyceride having esters of medium chain fatty acids. In some embodiments, the solubilizing agent is not peanut oil.

In some embodiments, oils used to solubilize estradiol and to suspend, partially suspend and partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In some embodiments, the medium chain fatty acids are C6, C8, C10, C12, C6-C12, C8-C12, C6-C10, C8-C10, or C10-C12 fatty acids. In some embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 50% saturated, greater than about 60% saturated, or greater than about 75% saturated. In some embodiments, a solubilizing agent comprises predominantly medium chain length, saturated fatty acids or derivatives thereof, specifically predominantly C8 to C12 saturated fatty acids or derivatives thereof.

In some embodiments, medium chain solubilizing agents include, for example and without limitation, saturated medium chain fatty acids or derivatives of saturated medium chain fatty acids: caproic acid (C6), enanthic acid (C7), caprylic acid (C8), pelargonic acid (C9), capric acid (C10), undecylic acid (C11), lauric acid (C12), tridecylic acid (C13), or myristic acid (C14). In some embodiments, the solubilizing agent comprises oils made of these free medium chain fatty acids, oils of medium chain fatty acid esters of glycerin, propylene glycol, or ethylene glycol, or combinations thereof. These examples comprise predominantly saturated medium chain fatty acids (i.e., greater than 50% of the fatty acids are medium chain saturated fatty acids). In some embodiments, the solubilizing agent comprises predominantly C6 to C12 saturated fatty acids or derivatives of fatty acids.

In some embodiments, the solubilizing agent comprises one or more mono-, di-, or triglycerides or combinations thereof. Exemplary glycerin based solubilizing agents include MIGLYOLs®, which are caprylic/capric triglycerides (SASOL Germany GmbH, Hamburg). MIGLYOLs® includes MIGLYOL® 810 (caprylic/capric triglyceride), MIGLYOL® 812 (caprylic/capric triglyceride), MIGLYOL® 816 (caprylic/capric triglyceride), and MIGLYOL® 829 (caprylic/capric/succinic triglyceride). Other caprylic/capric triglyceride solubilizing agents are likewise contemplated, including, for example: caproic/caprylic/capric/lauric triglycerides; caprylic/capric/linoleic triglycerides; or caprylic/capric/succinic triglycerides. Other exemplary caprylic/capric mono-, di-, or triglyceride solubilizing agents include CAPMULs® (ABITEC, Columbus, Ohio), including, but are not limited to, CAPMUL® MCM, CAPMUL® MCM C10, CAPMUL® MCM C8, CAPMUL® MCM C8 EP, and CAPMUL® 708 G. Other mono-, di-, and triglycerides of fractionated vegetable fatty acids, and combinations or derivatives thereof can be the solubilizing agent, according to embodiments. For example, the solubilizing agent can be 1,2,3-propanetriol (glycerol, glycerin, glycerine) esters of saturated coconut and palm kernel oil and derivatives thereof.

In some embodiments, the solubilizing agent comprises one or more esters of propylene glycol, polyethylene glycol, or combinations thereof. Exemplary propylene and polyeth-

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ylene glycol based solubilizing agents include glyceryl mono- and di-caprylates; propylene glycol monocaprylate (e.g., CAPMUL® PG-8 or CAPMUL® PG-8 NF); propylene glycol monocaprate (e.g., CAPMUL® PG-10); propylene glycol monolaurate (e.g., CAPMUL® PG-12 EP/NF); propylene glycol mono- and dicaprylates; propylene glycol mono- and dicaprate; propylene glycol dicaprylate/dicaprate (e.g., MIGLYOL® 840); propylene glycol dilaurate (e.g., CAPMUL® PG-2L EP/NF); diethylene glycol mono ester (e.g., TRANSCUTOL®, 2-(2-Ethoxyethoxyl)ethanol, GATTEFOSSÉ SAS, Saint-Priest, France); and diethylene glycol monoethyl ether.

In some embodiments, commercially available fatty acid glycerol and glycol ester solubilizing agents are prepared from natural oils and therefore may comprise components in addition to the fatty acid esters that predominantly comprise and characterize the solubilizing agent. Such other components may be, e.g., other fatty acid mono-, di-, and triglycerides, fatty acid mono- and diester ethylene or propylene glycols, free glycerols or glycols, or free fatty acids. For example, the Technical Data Sheet by ABITEC for CAPMUL® MCM C8 describes CAPMUL® MCM C8 as being composed of mono- and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as $\leq 1\%$ C6, $\geq 95\%$ C8, $\leq 5\%$ C10, and $\leq 1.5\%$ C12 and higher. By way of further example, MIGLYOL® 812 is generally described as a C8-C10 triglyceride because the fatty acid composition is at least about 80% caprylic (C8) acid and capric (C10) acid. However, it can also comprise small amounts of other fatty acids, e.g., less than about 5% of caproic (C6) acid, lauric (C12) acid, and myristic (C14) acid.

In some embodiments, the pharmaceutical composition comprises about 20% to about 85% solubilizing agent by weight, e.g., about 60% to about 85% solubilizing agent by weight. In some embodiments, the composition comprises progesterone, e.g., dissolved and micronized, from about 20 to about 50 wt %, e.g., about 30 to about 35 wt %. In some embodiments, the composition comprises estradiol from about 0.1 to about 0.8 wt %, e.g., about 0.15 to about 0.40 wt %.

Surfactants

In some embodiments, the pharmaceutical composition further comprises one or more non-ionic or ionic surfactants. In some embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of medium chain fatty acids or long chain fatty acids, for example, lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides, commercially available as GELUCIRE®, including, for example, GELUCIRE® 39/01 (glycerol esters of saturated C12-C18 fatty acids); GELUCIRE® 43/01 (hard fat NF/JPE); GELUCIRE® 44/14 (lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, lauroyl polyoxylglycerides (USA FDA IIG)); and GELUCIRE® 50/13 (stearoyl macrogol-32 glycerides EP, stearoyl polyoxyl-32 glycerides NF, stearoyl polyoxylglycerides (USA FDA IIG)).

In some embodiments, non-ionic surfactants comprise combinations of mono- and di-propylene and ethylene glycols and mono-, di-, and triglyceride combinations. For example, in some embodiments, polyethylene glycol glyceride (GELUCIRE®, GATTEFOSSÉ SAS, Saint-Priest, France) can be used herein as the surfactant. For example, GELUCIRE® 44/14 (PEG-32 glyceryl laurate EP), a medium chain fatty acid esters of polyethylene glycol, is a polyethylene glycol glyceride composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

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In some embodiments, non-ionic surfactants include, for example and without limitation: one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In some embodiments, non-ionic surfactants comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids.

In some embodiments, non-ionic surfactants include PEG-6 palmitostearate and ethylene glycol palmitostearate, which are available commercially as TEFOSE® 63 (GATTEFOSSÉ SAS, Saint-Priest, France), which can be used with, for example, CAPMUL® MCM having ratios of MCM to TEFOSE® 63 of, for example, 8:2 or 9:1. Other exemplary solubilizing agents/non-ionic surfactants combinations include, without limitation: MIGLYOL® 812:GELUCIRE 50/13 or MIGLYOL® 812:TEFOSE® 63.

A non-ionic or ionic surfactant may be used at concentrations greater than about 0.01%, for example at a concentration of about 0.01%-10.0%, about 0.1% to 10.0%, or about 1% to 10.0%. In some embodiments, the pharmaceutical composition comprises about 10.0% surfactant by weight. In some embodiments, the pharmaceutical composition comprises about 0.1% to about 5.0% surfactant by weight, e.g., about 1.0 wt %.

Other Excipients

In some embodiments, the pharmaceutical composition further comprises one more other excipients, such as but not limited to colorants, flavoring agents, preservatives, and taste-masking agents. The choice of excipients will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipients on solubility and stability, and the nature of the dosage form. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

Generally, the solubilizing agents, surfactants, and excipients used in the pharmaceutical compositions described herein are non-toxic, pharmaceutically acceptable, compatible with each other, and maintain stability of the pharmaceutical composition and the various components with respect to each other. Additionally, the combination of various components that comprise the pharmaceutical compositions will maintain will result in the desired therapeutic effect when administered to a subject.

Formulation

In some embodiments, combinations of solubilizing agents (e.g., two or more oils) or combinations of one or more solubilizing agents and one or more surfactants are used to form estradiol and progesterone compositions. Various ratios of these solubilizing agents or solubilizing agents and surfactants can be used. For example, CAPMUL® MCM and a non-ionic surfactant, e.g., GELUCIRE® 44/14 (lauroyl macrogol-32 glycerides EP; lauroyl polyoxyl-32 glycerides NF; lauroyl polyoxylglycerides (USA FDA IIG)), can be used at ratios of about 99:1 to about 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. As another example, CAPMUL® MCM and a non-ionic surfactant, e.g., TEFOSE® 63, can be used as ratios of about 8:2 or 9:1. Other exemplary solubilizing agent/surfactant combinations include, without limitation: MIGLYOL® 812:GELUCIRE® 50/13 or MIGLYOL® 812:TEFOSE® 63. The ratios of oil (e.g., medium chain fatty acid esters of mono-glycerides and diglycerides) to non-ionic surfactant can be

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significantly higher. For example, CAPMUL® MCM and GELUCIRE® can be used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1.

In some embodiments, estradiol or progesterone is soluble in the solubilizing agent at room temperature, although it may be desirable to warm certain solubilizing agents. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., CAPMUL® MCM) and polyethylene glycol glycerides (e.g., GELUCIRE®) as a surfactant, the oil or the surfactant can be warmed up, e.g., to about 65° C. for the surfactant and less for the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature, or at lower temperatures as the mixture cools, e.g., about 40° C. or about 30° C., or even after the mixture has cooled to room temperature. The progesterone can also be added as the mixture cools, e.g., to below about 40° C. or to below about 30° C., or after the mixture has cooled to room temperature.

As a non-limiting example, a composition of this disclosure comprises solubilized estradiol; progesterone, at least 30% (e.g., at least about 30%, about 40%, about 50%, about 60%, about 70%, about 75%, about 80%, about 85%, or more) of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein); and a solubilizing agent that is an oil, wherein the oil comprises medium chain fatty acid mono-, di-, or triglycerides, with or without a surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with CAPMUL® MCM NF (glyceryl caprylate/caprate) as a solubilizing agent and GELUCIRE® 44/14 (lauroyl polyoxyglyceride) as a surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following five formulations A-E:

TABLE 1

Pharmaceutical Composition A - progesterone 50 mg/estradiol 0.25 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.17	0.26
CAPMUL ® MCM, NF	65.49	98.24
GELUCIRE ® 44/14, NF	1.00	1.50
Total	100.00	150.00

TABLE 2

Pharmaceutical Composition B - progesterone 50 mg/estradiol 0.5 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.35	0.52
CAPMUL ® MCM, NF	65.32	97.98
GELUCIRE ® 44/14, NF	1.00	1.50
Total	100.00	150.00

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TABLE 3

Pharmaceutical Composition C - progesterone 100 mg/estradiol 0.5 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.17	0.52
CAPMUL ® MCM, NF	65.49	196.48
GELUCIRE ® 44/14, NF	1.00	3.00
Total	100.00	300.00

TABLE 4

Pharmaceutical Composition D - progesterone 100 mg/estradiol 1 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.34	1.03
CAPMUL ® MCM, NF	65.32	195.97
GELUCIRE ® 44/14, NF	1.00	3.00
Total	100.00	300.00

*Note:
1.00 mg Estradiol is equivalent to 1.03 mg Estradiol Hemihydrate

TABLE 5

Pharmaceutical Composition E - progesterone 200 mg/estradiol 2 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate	0.34	2.06
CAPMUL ® MCM, NF	65.32	391.94
GELUCIRE ® 44/14, NF	1.00	6.00
Total	100.00	600.00

In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono-, di-, or triglycerides, such as CAPMUL® MCM, and 0.5 to 10 wt % of a non-ionic surfactant, such as GELUCIRE® 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opaint red and white, and, optionally, MIGLYOL® 812.

Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g., at least about 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% or more, is solubilized appear to provide improved PK-related properties.

Pharmacokinetic Parameters of Estradiol and Progesterone Compositions

The pharmaceutical compositions of this disclosure can be formulated to provide desirable pharmacokinetic parameters in a subject (e.g., a female subject) to whom the composition is administered. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for progesterone in the

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subject. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for estradiol in the subject. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for one or more metabolites of progesterone or estradiol in the subject, for example, estrone or total estrone.

Following the administration of a composition comprising progesterone and estradiol to a subject, the concentration and metabolism of progesterone or estradiol can be measured in a sample (e.g., a blood, serum, or plasma sample) from the subject. Progesterone is metabolized to pregnanediols and pregnanones, which are then conjugated to glucuronide and sulfate metabolites that are excreted or further recycled. Estradiol is converted reversibly to estrone, and both estradiol and estrone can be converted to the metabolite estriol. In postmenopausal women, a significant proportion of circulating estrogens exist as sulfate conjugates, especially estrone sulfate. Thus, estrone can be measured with respect to "estrone" amounts (excluding conjugates such as estrone sulfate) and "total estrone" amounts (including both free, or unconjugated, estrone and conjugated estrone such as estrone sulfate).

The pharmaceutical compositions of this disclosure can be characterized for one or more pharmacokinetic parameters of progesterone, estradiol, or a metabolite thereof following administration of the composition to a subject or to a population of subjects. These pharmacokinetic parameters include AUC, C_{max} , and T_{max} . AUC is a determination of the area under the curve (AUC) plotting the blood, serum, or plasma concentration of drug along the ordinate (Y-axis) against time along the abscissa (X-axis). AUCs are well understood, frequently used tools in the pharmaceutical arts and have been extensively described. C_{max} is well understood in the art as an abbreviation for the maximum drug concentration in blood, serum, or plasma of a subject. T_{max} is well understood in the art as an abbreviation for the time to maximum drug concentration in blood, serum, or plasma of a subject.

In some embodiments, one or more pharmacokinetic parameters, e.g., AUC, C_{max} , or T_{max} , is measured for estradiol. In some embodiments, one or more pharmacokinetic parameters, e.g., AUC, C_{max} , or T_{max} , is measured for progesterone. In some embodiments, one or more pharmacokinetic parameters, e.g., AUC, C_{max} , or T_{max} , is measured for estrone. In some embodiments, one or more pharmacokinetic parameters, e.g., AUC, C_{max} , or T_{max} , is measured for total estrone.

Any of a variety of methods can be used for measuring the levels of progesterone, estradiol, estrone, or total estrone in a sample, including immunoassays, mass spectrometry (MS), high performance liquid chromatography (HPLC) with ultraviolet fluorescent detection, liquid chromatography in conjunction with mass spectrometry (LC-MS), tandem mass spectrometry (MS/MS), and liquid chromatography-tandem mass spectrometry (LC-MS/MS). In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured using a validated LC-MS/MS method. Methods of measuring hormone levels are well described in the literature.

The levels of progesterone, estradiol, estrone, or total estrone can be measured in any biological sample, e.g. a tissue or fluid such as blood, serum, plasma, or urine. In some embodiments, the sample is blood or plasma. In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured about 0.0, 0.10, 0.20, 0.05, 0.30, 0.35, 0.40, 0.45, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15,

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18, 21, 24, 27, 30, 33, 36, 39, 42, 45, or 48 hours after dosing, or any other appropriate time period that is common or useful in determining the levels of each of the hormones. In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of a single dose or a first dose. Generally, assays to determine the levels of progesterone, estradiol, estrone, or total estrone are measured one or more times every 5, 10, 15, 20, 30, 60, 120, 360, 480, 720, or 1440 minutes after administration, or combinations thereof (e.g., the first measurements are taken every 15 minutes for the first hour, followed by every 120 minutes thereafter). In embodiments, the timing of such measurements are designed to accurately measure C_{max} , T_{max} , or AUC. Timing can be adjusted based on the given circumstances (i.e., one formulation may cause a more rapid C_{max} , in which case the initial times would be clustered closer together, closer to time zero, or both to ensure accurate measurement of C_{max} , T_{max} , and AUC). In some embodiments, the C_{max} , T_{max} , or AUC values for progesterone, estradiol, estrone, or total estrone are measured following administration of a single dose of a pharmaceutical composition as described herein.

In some embodiments, the values for C_{max} , T_{max} , or AUC represent a number of values taken from all the subjects in a patient population and are, therefore, mean values (e.g., arithmetic or geometric means) averaged over the entire population.

In some embodiments, oral administration of a pharmaceutical composition comprising estradiol, progesterone, and a medium chain solubilizing agent as described herein to a subject, or to a population of subjects, produces one or more AUC, C_{max} , or T_{max} parameters, or one or more mean AUC, mean C_{max} , or mean T_{max} parameters, respectively, for estradiol, progesterone, estrone, or total estrone as described below.

AUC C_{max} , and T_{max} Parameters (A)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 0.25 mg and progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation A in Table 1 above.

In some embodiments, administration of a composition comprising about 0.25 mg estradiol and about 50 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; or
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml, and a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone

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that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, and a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml;
- (ii) a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; or
- (iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml;

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- (ii) a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml; or

- (iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml, a mean C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, a mean C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml, a mean C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml, a mean C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, methods of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation A in Table 1 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation A in Table 1 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone;

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wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; or a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

AUC , C_{max} , and T_{max} Parameters (B)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation B in Table 2 above.

In some embodiments, administration of a composition comprising about 0.50 mg estradiol and about 50 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; or
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, and a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, and a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

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In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml;
- (ii) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; or
- (iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml;
- (ii) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; or
- (iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, a mean C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, a mean C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819

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ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, a mean C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, a mean C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, methods of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation B in Table 2 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation B in Table 2 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

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AUC , C_{max} , and T_{max} Parameters (C)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation C in Table 3 above.

In some embodiments, administration of a composition comprising about 0.50 mg estradiol and about 100 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; or
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, and a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, and a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the

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subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml;
- (ii) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; or
- (iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml;
- (ii) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; or
- (iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood and plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, a mean C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, a mean C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, a mean C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, a mean C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, method of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation

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C in Table 3 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation C in Table 3 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

AUC , C_{max} , and T_{max} Parameters (D)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 1 mg and progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation D in Table 4 above.

In some embodiments, administration of a composition comprising about 1 mg estradiol and about 100 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml; or
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml, and a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

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- (i) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, and a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml;
- (ii) a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; or
- (iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

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In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml;
- (ii) a C_{max} for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml; or
- (iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml, a mean C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, a mean C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml, a mean C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml, a mean C_{max} for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, method of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation D in Table 4 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml; a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml; a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml; a C_{max} for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the

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pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation D in Table 4 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg-hr/ml to 877.3333 pg-hr/ml; a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng-hr/ml to 75.0543 ng-hr/ml; a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg-hr/ml to 5685.0567 pg-hr/ml; a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng-hr/ml to 126.0953 ng-hr/ml; and a C_{max} for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

AUC, C_{max} , and T_{max} Parameters (E)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 2 mg and progesterone at a dosage of about 200 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation E in Table 5 above.

In some embodiments, administration of a pharmaceutical composition comprising about 2 mg estradiol and about 200 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml; or
- (ii) a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml, and a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml; or
- (ii) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml, and a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml;
- (ii) a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml; or
- (iv) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the

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subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml;
- (ii) a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml; or
- (iv) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 7277 pg-hr/ml to 11370 pg-hr/ml;
- (ii) a C_{max} for estrone that is from 341 pg/ml to 533 pg/ml; or
- (iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for total estrone that is from 161 ng-h/ml to 252 ng-h/ml
- (ii) a C_{max} for total estrone that is from 28 ng/ml to 44 ng/ml; or
- (iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 2 mg estradiol and about 200 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml, a mean C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml, a mean C_{max} for progesterone that is from 71 ng/ml

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to 112 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 7277 pg-hr/ml to 11370 pg-hr/ml, a mean C_{max} for estrone that is from 341 pg/ml to 533 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 161 ng-h/ml to 252 ng-h/ml, a mean C_{max} for total estrone that is from 28 ng/ml to 44 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, method of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 2 mg estradiol and about 200 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation E in Table 5 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml; a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml; a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 7277 pg-hr/ml to 11370 pg-hr/ml; a C_{max} for estrone that is from 341 pg/ml to 533 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 161 ng-h/ml to 252 ng-h/ml; a C_{max} for total estrone that is from 28 ng/ml to 44 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation E in Table 5 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml; a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml; a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 7277 pg-hr/ml to 11370 pg-hr/ml; a C_{max} for estrone that is from 341 pg/ml to 533 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 161 ng-h/ml to 252 ng-h/ml; and a C_{max} for total estrone that is from 28 ng/ml to 44 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

In some embodiments, administration of the pharmaceutical composition as described herein results in the blood plasma estradiol concentration profile of FIG. 1. In some embodiments, administration of the pharmaceutical composition results in the blood plasma progesterone concentration profile of FIG. 2. In some embodiments, administration of

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the pharmaceutical composition results in the blood plasma estrone concentration profile of FIG. 3. In some embodiments, administration of the pharmaceutical composition results in the blood plasma total estrone concentration profile of FIG. 4.

Administration and Treatment

Pharmaceutical compositions comprising estradiol and progesterone as described herein (e.g., compositions comprising solubilized estradiol, suspended progesterone, and a medium chain solubilizing agent) can be prepared and administered in a wide variety of oral, parenteral and topical dosage forms. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Pharmaceutical compositions can be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, intrathecal, rectal, vaginal, sublingual or parenteral administration, including subcutaneous, intravenous, intramuscular, intrasternal, intracavernous, intrameatal, or intraurethral injection or infusion. In some embodiments, administration is by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally.

For preparing pharmaceutical compositions from the compounds of this disclosure, the pharmaceutically acceptable compositions can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid preparation can comprise one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Mack Publishing Co, Easton Pa. ("Remington's").

In general, the type of composition is selected based on the mode of administration. A pharmaceutical composition (e.g., for oral administration or delivery by injection) can be in the form of a liquid (e.g., an elixir, syrup, solution, emulsion or suspension). Alternatively, a pharmaceutical composition as described herein can take the form of a pill, tablet, or capsule containing the liquid oil, and thus, the composition can contain any of the following: a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose and derivatives thereof. The composition can also be formulated into a suppository disposed, for example, in a polyethylene glycol (PEG) solubilizing agent.

Administration of the compositions of this disclosure can be carried out via any of the accepted modes of administration. Thus, administration can be, for example, intravenous, topical, subcutaneous, transcutaneous, transdermal, intramuscular, oral, intra-joint, parenteral, intra-arteriole, intradermal, intraventricular, intracranial, intraperitoneal, intralesional, intranasal, rectal, vaginal, or by inhalation. In some embodiments, a composition as described herein is administered orally. For example, a pharmaceutical composition as described herein can be administered via capsules such as soft capsules.

In some embodiments, a pharmaceutical composition as described herein is administered once daily for a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100 days or more. In some embodiments, a pharmaceutical composition as

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described herein is administered daily for at least one week, at least two weeks, at least three weeks, at least four weeks, at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, at least twelve months, or more. In some embodiments, a pharmaceutical composition as described herein is administered as a continuous-combined therapy regimen.

In some embodiments, a 28-day or monthly regimen of daily doses is packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. In some embodiments, each daily dose contains both estradiol and progesterone. In some embodiments, one or more of the daily doses contains no estradiol or no progesterone. Daily doses that comprise no estradiol or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating the blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized or partially solubilized, or fully solubilized progesterone or solubilized estradiol in amounts as set forth herein, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of daily doses.

In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating conditions in subjects caused, at least in part, by estrogen deficiency, particularly for women with a uterus. For example, in embodiments, the pharmaceutical compositions disclosed herein are useful for the treatment of one or more of the following conditions: endometrial hyperplasia; secondary amenorrhea; prevention of preterm birth, when the subject has a shortened cervix; menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental progesterone or estrogen. In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating vasomotor symptoms, including but not limited to, hot flashes and night sweats. In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating hot flashes and night sweats. In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating hot flashes. Thus, in some embodiments, this disclosure provides methods of treating such a condition by administering to the subject a composition comprising estradiol and progesterone as described herein.

III. EXAMPLES

The following examples are offered to illustrate, but not to limit, the claimed subject matter.

Example 1

In an exemplary embodiment, a soft gelatin capsule contains a pharmaceutical composition comprising suspended progesterone and solubilized estradiol:

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TABLE 6

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL® MCM, NF		82.57	577.97
GELUCIRE® 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

The encapsulated pharmaceutical composition of Table 6 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas (N₂). Mixing or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL® MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.±2° C. GELUCIRE® 44/14 may be added to the CAPMUL® MCM and mixed until dissolved (to increase the solubility of progesterone in the final solution, GELUCIRE® 44/14 was added at about 10% w/w). The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the GELUCIRE® 44/14 and the CAPMUL® MCM.

Heat may be removed from the GELUCIRE® 44/14 and CAPMUL® MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the GELUCIRE® 44/14, CAPMUL® MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 2

An example of the final scale-up formulation is provided in Table 7. To manufacture, CAPMUL® MCM is heated to 40° C. GELUCIRE® 44/14 is heated to 65° C. and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until fully suspended.

TABLE 7

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL® MCM, NF		82.57	577.97	5.78
4.	GELUCIRE® 44/14, NF		10.0	70.00	0.70
Total:		100.00	700.00	7.00	

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Example 3

In an exemplary embodiment, a soft gelatin capsule contains a pharmaceutical composition having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 8

Item No.	Ingredient	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL® MCM, NF		73.371	146.74	1467.42
4.	GELUCIRE® 44/14, NF		1.500	3.00	30.00
Total:		100.000	200.00 mg	2000.00	

To manufacture, CAPMUL® MCM is heated to 65° C. GELUCIRE® 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 4

In an exemplary embodiment, a soft gelatin capsule contains a pharmaceutical composition having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 9

Item No.	Ingredient	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	CAPMUL® MCM, NF		65.32	391.93	3919.3
4.	GELUCIRE® 44/14, NF		1.00	6.0	60.0
Total:		100.00	600.0 mg	6000.0	

To manufacture, CAPMUL® MCM is heated to 65° C. GELUCIRE® 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resulting pharmaceutical composition is encapsulated in soft gelatin capsules. Alternatively, GELUCIRE® 44/14 is heated to 65° C. and CAPMUL® MCM is heated to 40° C.±5° C. to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 40° C.; the mixture is then passed through a colloid mill one or more times, e.g., three times.

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Example 5

Pharmacokinetics of the First Combination 17β-Estradiol/ Progesterone Capsule in Clinical Development for Hormone Therapy

The objective of this study was to evaluate the pharmacokinetic and oral bioavailability of a combination capsule of 17β-estradiol/progesterone in comparison to co-administration of the individual products ESTRACE® and PROMETRIUM®.

Subjects and Study Design:

An open label, balanced, randomized, single-dose, 2-treatment, 3-period, 3-sequence, crossover, partial-replicate, reference-scaled, oral, relative bioavailability study compared the bioavailability of an investigational 2-mg 17β-estradiol/200-mg progesterone combination capsule, without peanut oil (formulated in a manner similar to that set forth in Table 9), with that of co-administered 200-mg PROMETRIUM® (progesterone) and 2-mg ESTRACE® (17β-estradiol) tablets in healthy postmenopausal women aged 40-65 years (N=66). Key inclusion criteria for subjects included a BMI 18.50 to 29.99 kg/m² who were nonsmokers or ex-smokers (no smoking in the last 3 months). Key exclusion criteria for subjects included consuming grapefruit juice or poppy-containing foods within 48 hours before and throughout the study, use of any hormonal agent within 14 days before the study, and use of menopausal hormone therapy within 6 months before dosing.

Patients were randomly assigned sequentially to 1 of 3 dosing sequences of the same dose of the combination capsule (Test, T) and reference products (Reference, R): TRR, RTR, or RRT. 66 subjects were randomized and 62 (94.0%) completed the study. Subjects had a mean age of 49.5±5.6 years (range 40 to 64) and a mean BMI of 24.8±3.1 kg/m² (range 18.7-29.9).

After consuming a high-fat, high-calorie breakfast, each woman received a single dose of the combination (Test) capsule in 1 period of the study and single doses of the co-administered products (Reference) in each of the 2 remaining periods. Blood samples were collected within 75 minutes before dosing and post-dose at 0.25, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, and 48 hours after dosing to determine progesterone, free (unconjugated) estradiol, and free and total (conjugated+free, including estrone sulfates) estrone concentrations. After collection of blood samples at each time point, the blood samples were centrifuged at 4000 RPM for 10 minutes at 4° C. to separate the plasma. The plasma from samples was separated into two aliquots. 1.5 mL from the plasma sample was transferred into aliquot I, and the remaining plasma sample was transferred into aliquot II. These aliquots were stored at -30° C. for interim storage, then at -70° C. until completion of the analysis.

Progesterone, estradiol, estrone, and total estrone in human plasma was determined using the LC-MS/MS method. The primary (C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$) and secondary (T_{max} , $t_{1/2}$, and K_e) PK parameters for each analyte were determined for each subject during each period by non-compartment analyses using baseline-adjusted concentrations. Statistical analyses were conducted using the SAS® statistical software.

Results: The mean, standard deviation (SD), geometric mean, coefficient of variation (CV %), minimum, median, and maximum were calculated for C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} , $t_{1/2}$, K_e , K_{el_lower} , K_{el_upper} , and $AUC_{\%Extrap_obs}$ for progesterone, estradiol, estrone, and total estrone. The results are presented in Tables 10, 11, 12, and 13 below. For each of Tables 10-13, "Test Product (T)" refers to the progesterone+estradiol pharmaceutical composition, while "Reference product (R1)" and "Reference product (R2)" refers to co-administered PROMETRIUM® (progesterone) and ESTRACE® (estradiol). Blood plasma concentrations of progesterone, estradiol, estrone, and total estrone over time are also shown in FIGS. 1-4.

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TABLE 10

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R ₁ , R ₂) for Progesterone						
Untransformed Data (Mean ± SD)						
PK Parameter	N	Test Product (T)	N	Reference product (R1)	N	Reference product (R2)
C _{max} (ng/mL)	62	89.2222 ± 149.7309	62	72.7228 ± 101.8885	62	69.7590 ± 87.0777
AUC _{0-t} (ng · hr/mL)	62	120.0869 ± 164.1385	62	125.9406 ± 152.3483	62	111.5867 ± 113.3200
AUC _{0-∞} (ng · hr/mL)	57	131.3817 ± 172.4806	57	142.1332 ± 160.4853	56	126.6006 ± 117.2665
T _{max} (hr)	62	3.00 (0.83-10.00)	62	3.00 (1.00-12.00)	62	4.00 (0.67-18.00)
K _{el} (hr ⁻¹)	57	0.3064 ± 0.2427	57	0.2684 ± 0.1912	56	0.2795 ± 0.2475
t _{1/2} (hr)	57	4.6445 ± 4.5366	57	5.1555 ± 4.9794	56	5.0389 ± 4.5887
K _{el_Lower} (hr ⁻¹)	57	7.6667 ± 4.6047	57	7.4123 ± 4.2164	56	7.9018 ± 3.9120
K _{el_Upper} (hr ⁻¹)	57	16.2218 ± 11.0051	57	19.1728 ± 12.3801	56	18.1975 ± 10.0858
AUC_Extra (%)	57	4.3374 ± 2.5528	57	4.8416 ± 3.7526	56	5.1868 ± 4.1434

*Expressed in terms of median (range)

TABLE 11

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R ₁ , R ₂) for Estradiol			
Untransformed Data (Mean ± SD)			
PK Parameter	Test Product (T)	Reference product (R1)	Reference product (R2)
C _{max} (pg/mL)	64.7902 ± 50.9833	69.1286 ± 33.0484	73.4236 ± 43.4077
AUC _{0-t} (pg · hr/mL)	1403.7333 ± 763.8136	1508.2206 ± 876.7390	1658.2502 ± 976.5556
AUC _{0-∞} (pg · hr/mL)	2459.4394 ± 4498.2737	2842.8805 ± 4582.6502	2110.9591 ± 1175.3995
T _{max} (hr)	9.00(0.50-36.00)	10.0(0.50-35.12)	10.00(0.25-36.60)
K _{el} (hr ⁻¹)	0.0438 ± 0.0197	0.0457 ± 0.0358	0.0464 ± 0.0338
t _{1/2} (hr)	31.9104 ± 95.9769	25.0908 ± 28.8346	20.8774 ± 12.0825
K _{el_Lower} (hr ⁻¹)	14.9472 ± 7.2715	14.9667 ± 7.0150	14.7953 ± 5.8774
K _{el_Upper} (hr ⁻¹)	45.3602 ± 6.3668	44.3277 ± 7.4003	43.8330 ± 7.6449
AUC_Extra (%)	22.8106 ± 16.6498	25.4773 ± 20.2911	24.9566 ± 16.4713

*Expressed in terms of median (range)

TABLE 12

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R ₁ , R ₂) for Free Estrone			
Untransformed Data (Mean ± SD)			
PK Parameter	Test Product (T)	Reference product (R1)	Reference product (R2)
C _{max} (pg/mL)	426.5492 ± 179.3303	455.5107 ± 189.448	467.2302 ± 207.4373
AUC _{0-t} (pg · hr/mL)	9096.0907 ± 4377.2730	10156.0282 ± 5140.5831	10507.3557 ± 5183.1289
AUC _{0-∞} (pg · hr/mL)	11994.9695 ± 6678.5468	13445.9048 ± 8699.4068	14066.2362 ± 7563.2370
T _{max} (hr)	5.50(0.83-36.00)	8.00(1.67-18.00)	10.00(1.67-18.00)
K _{el} (hr ⁻¹)	0.0399 ± 0.0146	0.0424 ± 0.0172	0.0406 ± 0.0209
t _{1/2} (hr)	20.3172 ± 9.4052	19.4595 ± 9.8711	20.7515 ± 9.3985
K _{el_Lower} (hr ⁻¹)	13.8443 ± 7.0649	14.8871 ± 6.6459	14.9194 ± 6.4485
K _{el_Upper} (hr ⁻¹)	46.0238 ± 5.5080	46.2547 ± 5.3060	46.2244 ± 5.3126
AUC_Extra (%)	21.2980 ± 11.2283	20.3648 ± 11.1060	21.8900 ± 11.8537

*Expressed in terms of median (range)

TABLE 13

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R ₁ , R ₂) for Total Estrone						
Untransformed Data (Mean ± SD)						
PK Parameter	N	Test Product (T)	N	Reference product (R1)	N	Reference product (R2)
C _{max} (ng/mL)	61	35.4289 ± 17.0856	61	19.8716 ± 7.4485	61	19.9048 ± 8.0288
AUC _{0-t} (ng · hr/mL)	61	201.7524 ± 94.2081	61	182.7729 ± 88.8386	61	199.8295 ± 94.9392
AUC _{0-∞} (ng · hr/mL)	61	213.2402 ± 104.6011	60	193.6387 ± 100.5831	56	203.0289 ± 81.4884
T _{max} (hr)	61	2.50 (0.67-7.00)	61	4.00 (1.33-18.00)	61	4.00 (1.33-10.00)

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TABLE 13-continued

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R ₁ , R ₂) for Total Estrone						
Untransformed Data (Mean ± SD)						
PK Parameter	N	Test Product (T)	N	Reference product (R1)	N	Reference product (R2)
K _{el} (hr ⁻¹)	61	0.0799 ± 0.0398	60	0.0803 ± 0.0399	56	0.0718 ± 0.0243
t _{1/2} (hr)	61	10.3619 ± 4.0023	60	9.8448 ± 3.0702	56	10.7830 ± 3.6624
K _{el, Lower} (hr ⁻¹)	61	13.0492 ± 6.8585	60	13.5945 ± 8.0129	56	11.8870 ± 6.8696
K _{el, Upper} (hr ⁻¹)	61	45.3979 ± 6.6589	60	46.3775 ± 5.2525	56	46.7054 ± 4.3888
AUC _{Extra} (%)	61	4.5030 ± 3.7366	60	4.5913 ± 3.4953	56	5.3450 ± 3.9831

*Expressed in terms of median (range)

Example 6

Pharmacokinetic data (C_{max}, AUC_(0-t), AUC_(0-∞), and T_{max}) for progesterone, estradiol, free estrone, and total estrone is presented in Tables 14-17. Pharmaceutical compositions A-E are disclosed in Tables 1-5. The pK values for pharmaceutical composition E were calculated as disclosed in Example 5. For pharmaceutical compositions A-D, expected pharmacokinetic data is calculated from the data disclosed for pharmaceutical composition E.

TABLE 14

Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Progesterone						
Pharmaceutical Composition	Progesterone Content	Estradiol Content	C _{max} (ng/mL)	AUC _(0-t) (ng · hr/mL)	AUC _(0-∞) (ng · hr/mL)	T _{max} (hr)
A	50 mg	0.25 mg	22.30555	30.0217	32.8454	3.00
B	50 mg	0.50 mg	22.3055	30.0217	32.8454	3.00
C	100 mg	0.50 mg	44.6111	60.0435	65.6909	3.00
D	100 mg	1 mg	44.6111	60.0435	65.6909	3.00
E	200 mg	2 mg	89.2222	120.0869	131.3817	3.00

TABLE 15

Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Estradiol						
Pharmaceutical Composition	Progesterone Content	Estradiol Content	C _{max} (pg/mL)	AUC _(0-t) (pg · hr/mL)	AUC _(0-∞) (pg · hr/mL)	T _{max} (hr)
A	50 mg	0.25 mg	8.0988	175.4667	307.4299	9.00
B	50 mg	0.50 mg	16.1976	350.9333	614.8599	9.00
C	100 mg	0.50 mg	16.1976	350.9333	614.8599	9.00
D	100 mg	1 mg	32.3951	701.8667	1229.7197	9.00
E	200 mg	2 mg	64.7902	1403.7333	2459.4394	9.00

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TABLE 16

Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Free Estrone						
Pharmaceutical Composition	Progesterone Content	Estradiol Content	C _{max} (pg/mL)	AUC _(0-t) (pg · hr/mL)	AUC _(0-∞) (pg · hr/mL)	T _{max} (hr)
A	50 mg	0.25 mg	53.3187	1137.0113	1499.3712	5.50
B	50 mg	0.50 mg	106.6373	2274.0227	2998.7424	5.50
C	100 mg	0.50 mg	106.6373	2274.0227	2998.7424	5.50
D	100 mg	1 mg	213.2746	4548.0454	5997.4848	5.50
E	200 mg	2 mg	426.5492	9096.0907	11994.9695	5.50

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TABLE 17

Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Total Estrone						
Pharmaceutical Composition	Progesterone Content	Estradiol Content	C _{max} (ng/mL)	AUC _(0-t) (ng · hr/mL)	AUC _(0-∞) (ng · hr/mL)	T _{max} (hr)
A	50 mg	0.25 mg	4.4286	25.2191	26.6550	2.50
B	50 mg	0.50 mg	8.8572	50.4381	53.3101	2.50
C	100 mg	0.50 mg	8.8572	50.4381	53.3101	2.50
D	100 mg	1 mg	17.7145	100.8762	106.6201	2.50
E	200 mg	2 mg	35.4289	201.7524	213.2402	2.50

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The ranges of expected pK values for each of the pharmaceutical compositions of Tables 1-4 are disclosed in Tables 18-21, respectively.

TABLE 18

pK Ranges for the Pharmaceutical Composition of Table 1 (Pharmaceutical Composition A)			
	C _{max}	AUC _(0-t)	AUC _(0-∞)
Progesterone	17.8444 ng/mL to 27.8819 ng/mL	24.0174 ng · hr/mL to 37.5272 ng · hr/mL	26.2763 ng · hr/mL to 41.0568 ng · hr/mL
Estradiol	6.4790 pg/mL to 10.1235 pg/mL	140.3733 pg · hr/mL to 219.3333 pg · hr/mL	245.9439 pg · hr/mL to 384.2874 pg · hr/mL
Free estrone	42.6549 pg/mL to 66.6483 pg/mL	909.6091 pg · hr/mL to 1421.2642 pg · hr/mL	1199.4970 pg · hr/mL to 1874.2140 pg · hr/mL

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TABLE 18-continued

pK Ranges for the Pharmaceutical Composition of Table 1 (Pharmaceutical Composition A)			
	C_{max}	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Total estrone	3.5429 ng/mL to 5.5358 ng/mL	20.1752 ng · hr/mL to 31.5238 ng · hr/mL	21.3240 ng · hr/mL to 33.3188 ng · hr/mL

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TABLE 19

pK Ranges for the Pharmaceutical Composition of Table 2 (Pharmaceutical Composition B)			
	C_{max}	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Progesterone	17.8444 ng/mL to 27.8819 ng/mL	24.0174 ng · hr/mL to 37.5272 ng · hr/mL	26.2763 ng · hr/mL to 41.0568 ng · hr/mL
Estradiol	12.9580 pg/mL to 20.2469 pg/mL	280.7467 pg · hr/mL to 438.6667 pg · hr/mL	491.8879 pg · hr/mL to 768.5748 pg · hr/mL
Free estrone	85.3098 pg/mL to 133.2966 pg/mL	1819.2181 pg · hr/mL to 2842.5283 pg · hr/mL	2398.9939 pg · hr/mL to 3748.4280 pg · hr/mL
Total estrone	7.0858 ng/mL to 11.0715 ng/mL	40.3505 ng · hr/mL to 63.0476 ng · hr/mL	42.6480 ng · hr/mL to 66.6376 ng · hr/mL

TABLE 20

pK Ranges for the Pharmaceutical Composition of Table 3 (Pharmaceutical Composition C)			
	C_{max}	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Progesterone	35.6889 ng/mL to 55.7639 ng/mL	48.0348 ng · hr/mL to 75.0543 ng · hr/mL	52.5527 ng · hr/mL to 82.1136 ng · hr/mL
Estradiol	12.9580 pg/mL to 20.2469 pg/mL	280.7467 pg · hr/mL to 438.6667 pg · hr/mL	491.8879 pg · hr/mL to 768.5748 pg · hr/mL
Free estrone	85.3098 pg/mL to 133.2966 pg/mL	1819.2181 pg · hr/mL to 2842.5283 pg · hr/mL	2398.9939 pg · hr/mL to 3748.4280 pg · hr/mL
Total estrone	7.0858 ng/mL to 11.0715 ng/mL	40.3505 ng · hr/mL to 63.0476 ng · hr/mL	42.6480 ng · hr/mL to 66.6376 ng · hr/mL

TABLE 21

pK Ranges for the Pharmaceutical Composition of Table 4 (Pharmaceutical Composition D)			
	C_{max}	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Progesterone	35.6889 ng/mL to 55.7639 ng/mL	48.0348 ng · hr/mL to 75.0543 ng · hr/mL	52.5527 ng · hr/mL to 82.1136 ng · hr/mL
Estradiol	25.9161 pg/mL to 40.4939 pg/mL	561.4933 pg · hr/mL to 877.3333 pg · hr/mL	983.7758 pg · hr/mL to 1537.1496 pg · hr/mL
Free estrone	170.6197 pg/mL to 266.5933 pg/mL	3638.4363 pg · hr/mL to 5685.0567 pg · hr/mL	4797.9878 pg · hr/mL to 7496.8559 pg · hr/mL
Total estrone	14.1716 ng/mL to 22.1431 ng/mL	80.7010 ng · hr/mL to 126.0953 ng · hr/mL	85.2961 ng · hr/mL to 133.2751 ng · hr/mL

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various

alternatives together with details of the structure and function of the devices or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the

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appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

What is claimed is:

1. A method of treating a subject having vasomotor symptoms associated with estrogen deficiency, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising:

about 0.25 mg estradiol, wherein at least 80% of the estradiol in the composition is solubilized estradiol; progesterone, wherein the progesterone comprises suspended progesterone; and

a medium-chain oil comprising medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids, and wherein the entire amount of the estradiol and the progesterone in the composition is present in the oil;

wherein administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an area under the curve $(AUC)_{(0-t)}$ for estradiol that is from 140.3733 pg-hr/ml to 219.3333 pg-hr/ml; and
(ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

2. The method of claim 1, wherein the subject is female.

3. The method of claim 1, wherein the subject is a woman having a uterus.

4. The method of claim 1, wherein administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg-hr/ml to 219.3333 pg-hr/ml and a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

5. The method of claim 1, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng-hr/ml to 37.5272 ng-hr/ml; and
(ii) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

6. The method of claim 1, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg-hr/ml to 1421.2642 pg-hr/ml; and
(ii) a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml.

7. The method of claim 1, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng-hr/ml to 31.5238 ng-hr/ml; and
(ii) a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

8. A method of treating a subject having vasomotor symptoms associated with estrogen deficiency, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising:

about 0.5 mg estradiol, wherein at least 80% of the estradiol in the composition is solubilized estradiol; progesterone, wherein the progesterone comprises suspended progesterone; and

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a medium-chain oil comprising medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids, and wherein the entire amount of the estradiol and the progesterone in the composition is present in the oil;

wherein administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an area under the curve $(AUC)_{(0-t)}$ for estradiol that is from 280.7467 pg-hr/ml to 438.6667 pg-hr/ml; and
(ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

9. The method of claim 8, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg-hr/ml to 2842.5283 pg-hr/ml; and
(ii) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml.

10. The method of claim 8, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng-hr/ml to 63.0476 ng-hr/ml; and
(ii) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

11. The method of claim 8, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng-hr/ml to 75.0543 ng-hr/ml; and
(ii) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

12. A method of treating a subject having vasomotor symptoms associated with estrogen deficiency, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising:

about 1 mg estradiol, wherein at least 80% of the estradiol in the composition is solubilized estradiol; progesterone, wherein the progesterone comprises suspended progesterone; and

a medium-chain (C6-C12) oil comprising medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids, and wherein the entire amount of the estradiol and the progesterone in the composition is present in the oil;

wherein administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an area under the curve $(AUC)_{(0-t)}$ for estradiol that is from 561.4933 pg-hr/ml to 877.3333 pg-hr/ml; and
(ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml.

13. The method of claim 12, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg-hr/ml to 5685.0567 pg-hr/ml; and

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- (i) a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml.

14. The method of claim 12, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml; and
 (ii) a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

15. The method of claim 8, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
 (ii) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

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16. The method of claim 12, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
 (ii) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

17. The method of claim 1, wherein the composition comprises about 0.25 mg estradiol and about 50 mg progesterone.

18. The method of claim 8, wherein the composition comprises about 0.5 mg estradiol and about 50 mg progesterone.

19. The method of claim 8, wherein the composition comprises about 0.5 mg estradiol and about 100 mg progesterone.

20. The method of claim 12, wherein the composition comprises about 1 mg estradiol and about 100 mg progesterone.

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